Physician Preferences for Medical Innovation

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Abstract

Health care spending growth challenges the budgets of governments, businesses, and families. In 2015, one in every six dollars spent in the U.S. economy was related to health care – twice the share in 1980. The rapid growth in health care spending leaves less room for other investments, and this pressure will only increase over time if these expenditures continue to grow as projected. Existing research has shown that innovations in medical technology (e.g., new drugs and procedures) drive health care spending growth. This dissertation explores the role physicians play in the integration of new treatments and procedures into the health care system. It examines physician preferences for new technologies, how these preferences change in response to information shocks, and proposes an approach to disentangle patient demand factors from physician-level proclivity for medical innovation.

Chapter one is a descriptive analysis of the utilization of a broad range of innovative medical technologies. It uses Medicare claims data to identify 46 medical technologies that were new or rapidly diffusing over 2005 to 2010, documents variation in utilization across provider organizations, and estimates correlations in utilization across these categories within provider organizations. There was substantial variation between provider organizations. The relationship in utilization across categories of technologies within provider organizations, however, was modest. These results suggest provider organizations do not broadly and consistently influence the utilization of all types of new medical technology. This implies that payment reforms focused

on provider organizations will likely have different effects on the utilization of new technology depending on the type of medical innovation.

Chapter two examines how physician preferences for drugs with uncertain benefits and risks change following a medical reversal of a drug already in use. In May 2007, evidence emerged of cardiovascular risk associated with Avandia (rosiglitazone), one of two products in the thiazolidinedione (TZD) class of oral anti-diabetics. In response, the FDA immediately issued a safety alert, and all drugs in the class were required to carry a black box warning on their labels discouraging use for certain patients. This study linked physicians' responses to this safety alert with their future prescribing of a new class of direct oral anticoagulants (DOACs). Like TZDs, when DOACs were first approved, there was not robust evidence that these new drugs were superior to the existing treatment. We first modeled the probability of prescribing drugs in the TZD class (among all diabetes prescriptions) before and after the safety alert using multi-level logistic regression models that included random effects for individual physicians' levels of prescribing relative to their peers. We next assessed the relationship between the physician-specific effects and use of DOACs. We found no difference in the use of DOACs based on how physicians responded to a safety alert for drugs in the TZD class. These results suggest that the effects of a medical reversal for pharmaceutical products do not spill over across drugs in different therapeutic areas. Additionally, consistent with previous studies, we found that physicians responded to a safety-related information shock for TZDs, but mostly confined their response to the affected drug. If this were to hold more generally, it suggests evidence can change physician behavior, but to do so broadly, each drug would require its own robust evidence.

Chapter 3 develops a framework for assessing the dimensions along which patients sort randomly to physicians. Many factors influence treatment decisions. Patient preferences pose a specific challenge because they are an input into physician decision-making and are also potentially correlated across types of services and treatments, as well as with outcomes, such as total spending. I examine using an instrumental variable (IV) approach defining a measure of physician preference for novel treatments that is plausibly unrelated to patient demand. The set of descriptive analyses and empirical tests presented in this chapter evaluate whether inclusion criteria used to define a study population selects a sample that is as good as randomly assigned – the key assumption in an IV approach. Once such a sample has been constructed, the relationship between a physician's practice patterns and the broader trends in the spending of their patients can be examined. I demonstrate how my proposed instrument performs in the context of prescription diabetes medications for patients receiving care from an endocrinologist.

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Chapter 1: Utilization of New Medical Technology Among Provider Organizations

INTRODUCTION

Over the last several decades there have been rapid advances in medical technology (National Center for Health Statistics, 2010). These advances have been accompanied by higher and continuously growing expenditures (Hartman et al., 2018). Providers play a central role in medical care decisions, including which new medical technologies to use, and are the focal point of recent efforts in the United States to lower health care spending growth. Yet, there has been little work examining the role of provider organizations in the integration of new medical technologies into the health care system. Under recent payment reforms, provider organizations bear risk for the total health care spending of their attributed patients. In this context, the implications for the adoption and use of new medical technology depend on the role provider organizations play in encouraging or discouraging utilization of innovative procedures, drugs, and practices. If provider organizations have unique footprints in the utilization of new technology, this would suggest an influence of organizational factors and efforts by provider organizations to reduce spending could have effects on the utilization of innovative medical care. If this is the case, describing the patterns in utilization across different types of new technologies prior to the introduction of payment reforms is useful for anticipating specific effects that may materialize in response. For example, physicians may have inconsistent preferences for different types of innovations, which may be modified by factors such as financial incentives. On the other hand, if we do not observe relationships in utilization across broad categories of new technology, then provider organizations may not be the best focal point for understanding the effects on the utilization of medical innovations because they have not thus far exerted influence across the board on the adoption of new technologies.

The consensus in the economics literature is that medical innovation is the primary driver of the growth in health care spending in the United States (Chernew & Newhouse, 2012a). Theoretically, new medical technologies could either raise or lower spending, depending on their effects on prices and utilization. In practice, most innovations seem to be cost increasing. New medical technologies are often more expensive than existing treatments or services (Kesselheim et al., 2016). Moreover, new medical technologies often increase utilization, either by expanding the conditions that can be screened for, diagnosed, and treated, or by expanding the population of people that can be served.[1] It may become possible to reach a broader population because the new technology lowers the unit cost, has a better side effect profile, or carries less risk for patients. A substantial portion of increasing health care expenditures observed over the last several decades is thus attributed to the continuous introduction of new medical technologies over that time (National Center for Health Statistics, 2010).

In the United States, growth in total health expenditures has consistently outpaced growth in the economy. In 2016, one in every six dollars spent in the U.S. economy was related to health care – twice the share in 1980 (Centers for Medicare & Medicaid Services, 2017). The rapid growth in health care spending leaves less room for other investments, and this pressure will only increase over time if these expenditures continue to grow as projected (Congressional Budget Office, 2017). While health care spending levels and growth are high overall, they also exhibit substantial variation across regions (Cubanski, Neuman, & White, 2015). Moreover, spending differences are not correlated with quality. That is, higher spending regions do not necessarily have better health outcomes.

[1] Consider an analysis of the cost of treating elderly heart attack patients, which found increases in the rate of cardiac catherization, bypass, and angioplasty, following the diffusion of new medical technologies involved in performing these procedures (Cutler & McClellan, 1996).

Research examining the role of new medical technology in health care spending growth generally takes one of two approaches. The first attempts to account for all other factors contributing to the growth in spending, including the expansion of insurance coverage, rising incomes, inflation, and demographic changes, and then attributes residual growth to technology (for example, Newhouse, 1992). The second approach tracks specific innovations or disease areas and examines how much new technology changed spending for particular treatments (for example, Cutler & McClellan, 1996). No analysis, however, has identified a broad set of new medical technologies and examined patterns of use by provider organizations. Similarly, while the literature examining the variation in spending and delivery of health care has a long history (Fisher et al., 2003a, 2003b; Glover, 1938; Wennberg & Gittelsohn, 1973), few papers have examined variation in utilization of new medical technologies across provider groups.[2] As a result, it is unknown whether provider organizations consistently use new technology across categories.

In this paper, we identified 46 medical technologies that were new or rapidly diffusing over 2005 to 2010 and used claims data for a 20 percent random sample of Medicare beneficiaries to examine patterns of use in 2011. We describe variation in utilization within and across provider organizations and types of technology. To do this, we applied hierarchical modeling techniques to examine patterns in use across provider organizations for two categories of technologies: Medicare Part A and B inpatient and outpatient services and Medicare Part D prescription drugs. We also examined patterns in three sub-categories of Part A and B services, including imaging, radiotherapy, and physician-administered drugs.

[2] An analysis of the diffusion of Bevicizumab across oncology practices found wide variation in the use of this new chemotherapy agent (Keating et al., 2018).

EMPIRICAL ANALYSIS

Overview

We used hierarchical models to examine utilization of new medical technologies by provider organizations, defined as the group of primary care physicians (PCPs) billing under the same tax identification number (TIN). The set of new medical technologies included prescription and physician-administered drugs approved between 2005 and 2010 and non-drug services that were new or rapidly diffusing in the Medicare population over 2005 to 2010. We restricted the set of new technologies to drugs and services that were relevant to the Medicare population and had broadly diffused by 2010 (see appendix 1 for additional details on selection criteria). Utilization was examined in 2011. We estimated the relationship between use in two pre-specified categories of technology – inpatient and outpatient services covered under Medicare Parts A and B and prescription drugs covered under the Part D prescription drug program. In addition, we examined three sub-categories of the Part A and B services – imaging, radiotherapy, and physician-administered drugs. We did not examine tests and procedures included in the broader set of Part A and B services because utilization in these categories was skewed and could not be reliably modeled using the methods described below. These categories align with financial incentives associated with the use of specific drugs and services. Within fee-for-service Medicare, prescription drugs, inpatient procedures, physician-administered drugs, and other outpatient services are reimbursed differently (Medicare Payment Advisory Commission, 2017b, 2017c, 2017d, 2017e). For example, physicians receive no direct payment when a patient fills a prescription for a drug covered by Part D; in contrast, physicians receive the amount on the physician fee schedule each time they provide a covered service under Part B and are reimbursed the average sales price (ASP) of the drug plus 6% for the provision of physician-administered

drugs. Thus, the payment system for Part B incentivizes providing a larger quantity of services and the use of higher priced drugs.

Data and Study Population

We analyzed claims for a 20 percent sample of Medicare beneficiaries using the inpatient, outpatient, carrier, and Part D drug event (PDE) files. We included elderly beneficiaries who could be attributed to a primary care physician billing under a tax identification number (TIN) in the carrier claims (see the appendix for additional details on attribution) and were enrolled in either Parts A and B or Part D for the entire year.[3] We were primarily interested in examining medium and large provider organizations, and thus restricted our sample to groups of physicians who had at least 200 attributed beneficiaries in 2011. All utilization for a beneficiary was attributed to their assigned TIN, even when a physician associated with a different TIN was on the claim.[4] Thus, our measure of utilization reflects a mix of the services provided within the formal provider organization and a latent network of specialists to which those physicians referred, or from which their patients otherwise sought care. Beneficiaries were assigned to denominator populations based on the presence of a relevant diagnosis for the drug or service in 2011. Enrollment in Part D was also required for eligibility for the prescription drug denominator populations (see appendix 1 for how diagnoses were determined). Table 1.1 lists the selected new technologies, the procedure codes used to identify these technologies in the claims, and the diagnoses codes used to identify beneficiaries eligible

[3] We also included beneficiaries who were only enrolled for part of the year and died during the year.
[4] Previous work has shown that patients attributed to lower spending PCPs have lower overall spending, including services not provided by the PCP (Mehrotra, Huckfeldt, Haviland, Gascue, & Sood, 2016). In addition, evaluation of spending and utilization for patients attributed to physicians that are part of Accountable Care Organizations includes all health care services those patients receive, whether or not it is provided by PCPs in the ACO or not (for example, see McWilliams, Chernew, Landon, & Schwartz, 2015 and McWilliams, Landon, & Chernew, 2013).

for the denominator populations. PCPs included physicians with specialty codes for internal medicine, family medicine, general practice, or gerontology.

Outcome Variable

We created indicator variables for each new technology in our set. These indicators were equal to 1 if a beneficiary had a claim for the service or drug during the year, and 0 otherwise.

Patient Characteristics

Information from the Medicare Beneficiary Summary File (MBSF) was used to determine age, sex, race and ethnicity, dual eligibility for Medicare and Medicaid, and whether disability or End Stage Renal Disease (ESRD) was the original reason for Medicare eligibility for each beneficiary in the sample. We assessed health status by summing the number of chronic conditions each beneficiary had in the year using the Chronic Conditions Warehouse segment of the MBSF. We also noted if the beneficiary died during the study year.

Variation and Patterns of Use Across Types of Technology

We used Fay-Herriot-type models (see Zaslavsky, 2007) to estimate relationships between provider organization-level measures of utilization for categories of new medical technologies. This three-step approach included estimating the case mix-adjusted utilization for

Table 1.1: List of Selected New Medical Technologies

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
Part A/B Inpatient and Outpatient Services		
Ablation	ICD-9: 3734	atrial fibrillation or flutter (427.3X)
Breast MRI	HCPCS: 77058, 77059, C8903, C8904, C9805, C9806, C9807, C9808	breast cancer (174.X); carcinoma in situ of breast and genitourinary system (233.X); benign mammary dysplasias (610.X); other disorders of the breast, excluding galactocele, ptosis, and hypoplasia (611.X and not 611.5, 611.81, 611.82); personal history of malignant neoplasm of breast (V10.3); family history of malignant neoplasm of breast (V16.3); nonspecific abnormal findings on radiological and other examination of breast (793.8X)
Brachytherapy	ICD-9: 9227, 9228; HCPCS: 0182T, 19296-19298, 55860, 55862, 55865, 55875, 55876, 77750, 77761-77763, 77776-77778, 77781-77790, 77799, 58346	skin (173.X), breast (174.X), cervical (180), uterine (182.X), prostate (185) cancer diagnosis; carcinoma in situ (233.X); encounter for radiotherapy (V58.0)
Calcium Score	HCPCS: 0144T, 75571	other/unspecified hyperlipidemia, pure hypercholesterolemia, mixed hyperlipidemia (272.0, 272.2, 272.4); hypertension (401.X); angina pectoris (413.X); coronary atherosclerosis of unspecified type of vessel, native or graft, or native coronary artery (414.00, 414.01); chest pain, shortness of breath (786.05, 786.5X); nonspecific abnormal results of function study of cardiovascular system (794.3X); family history of ischemic heart disease/cardiovascular disease(V17.3, V17.41, V17.49); screening for ischemic heart disease, for other and unspecified cardiovascular or respiratory conditions (V81.0, V81.2, V81.4)

Continued

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
Capsule Endoscopy	HCPCS: 91110, 91111, 91299	iron deficiency (280.X); acute posthemorrhagic anemia and other unspecified anemia(285.1, 285.9); regional enteritis (555.X); angiodysplasia of intestine (with and without hemorrhage), ulceration of intestine, and hemorrhage of rectum and anus (569.3, 569.82, 569.84, 569.85); gastrointestinal hemorrhage (578.X); diarrhea (787.91); abdominal pain, excluding left lower quadrant (789.0X and not 789.04); nonspecific abnormal findings in stool contents (792.1)
Cardiac Imaging - CTA, PET, MRI	HCPCS: 0146T, 0147T, 0148T, 0149T, 71275, 75574, 75557, 75558, 75560, 75562, 75564, 75559, 75561, 75563, 78459, 78491, 78492	symptoms involving respiratory system and other chest symptoms (786.X and not 786.4); other diseases of lung(518.X and not 518.2, 518.3, 518.53, 518.6, 518.7); other forms of ischemic heart disease (414.X); acute pulmonary heart disease(413.X); aortic aneurysm and dissection, except thoracic aneurysm without mention of rupture (441.X and not 441.2); pleurisy (511.X); nonspecific (abnormal) findings on radiological and other examination of body structure, except biliary tract and breast (793.X and not 793.3, 793.8X); nonspecific abnormal results of pulmonary or cardiovascular system function study(794.2 and 794.3X); cardiac dysrhythmias (427.X); emphysema (492.X)
Carotid Endovascular Stent	ICD-9: 0063	carotid artery occlusion and stenosis (433.1X)

Continued

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
CT Colonography	HCPCS: 0066T, 74263, 0067T, 74261, 74262	benign neoplasm of colon (211.3); iron deficiency anemias (280.0, 280.9); unspecified intestinal obstruction (560.9); diverticula of colon (562.1X); constipation, functional digestive disorders not elsewhere classified (564.00); other specified disorders of intestine (569.89); blood in stool, hemorrhage of gastrointestinal tract, unspecified (578.1, 578.9); other anomalies of intestine (751.5); other symptoms involving digestive system, diarrhea (787.91, 787.99); abdominal pain, unspecified site (789.00); nonspecific (abnormal) findings on radiological and other examination of gastrointestinal track (793.4); personal history of digestive disease (V12.7X and not V12.71)
Home Sleep Test	HCPCS: G0398, G0399, G0400	obstructive sleep apnea (327.23); sleep disturbances (780.5X)
H. Pylori Test – Breath and Stool	HCPCS: 78267, 78268, 83013, 83014, 22530, 22521	h. pylori (41.86), diseases of esophagus(530.X), peptic ulcer site unspecified (533.X), gastritis and duodenitis (535.X), disorders of function of stomach (536.X), symptoms involving digestive system (787.X), other symptoms involving abdomen and pelvis (789.X)
IGRA TB Test	HCPCS: 86480, 86481	all Medicare beneficiaries
Image-Guided Radiation Therapy	HCPCS: 77014, 76370, 77421, 0197T	encounter for radiotherapy (V58.0); Tongue (141.X), orophyrnx (146.X), esophogeal (150.X), rectal (154.X), pancreatic (157.X), larynx (161.X), lung (162.X), breast (174.X), uterine (182.X), prostate (185), and bladder (188.X) cancer

Continued

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
Intensity-Modulated Radiation Therapy	HCPCS: 77418, 0073T	encounter for radiotherapy (V58.0); Tongue (141.X), orophyrnx (146.X), esophogeal (150.X), rectal (154.X), pancreatic (157.X), larynx (161.X), lung (162.X), breast (174.X), uterine (182.X), prostate (185) cancer diagnosis; malignant neoplasm of other and ill-defined sites (195.X)
PET Scan (non-cardiac)	HCPCS: 78608, 78609, 78611 - 78616	esophageal (150.X), colorectal (153.X, 154.X), pancreatic (157.X), lung (162.X), skin (172.X) breast (174.X), ovarian (183.X), prostate (185), bladder (188.X), kidney (189.X), brain (191.X), other and ill-defined sites (195.X), lymphoid and histiocytic tissue (202.X) cancer diagnoses; multiple myeloma and immunoproliferative neoplasms (203.X); other diseases of the lung (518.0, 518.3, 518.4, 518.81, 518.89); symptoms involving respiratory system and other chest symptoms (786.X); nonspecific (abnormal) findings on radiological and other examination of body structure (793.X); observation for suspected malignant neoplasm (V71.1X)
Radiosurgery, Robotic	HCPCS: G0339, G0340	encounter for radiotherapy (V58.0); Pancreatic (157.X), lung (162.X), prostate (185), brain cancer (191.X); benign brain neoplasm (225.X)
Robot Assisted Prostatectomy	ICD-9: 1740-1745 and 1749	prostate cancer (185)
Physician-Administered Drugs		
Lucentis (ranibizumab)	HCPCS: J2778	macular degeneration (362.52)

Continued

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
Amphadase (hyaluronidase)	HCPCS: J3470	senile cataract (366.1X); pain in joint (719.4X); spondylosis and allied disorders (721.X); intervertebral disc disorders (722.X); other disorders of cervical region (723.X); other and unspecified disorders of back (724.X); eripheral enthesopathies and allied syndromes (726.x)
Firmagon (degarelix acetate)	HCPCS: J9155	prostate cancer (185)
Feraheme (ferumoxytol)	HCPCS: Q0138	chronic kidney disease (585.X); iron deficiency anemias (280.X); other and unspecified anemias (285.X)
Prescription Drugs		
Amitiza (lubiprostone)		constipation (564.X); abdominal pain (789.0X)
Bepreve (bepotastine besilate)		other retinal disorders (362.X); conjunctivitis (372.X); allergic rhinitis (477.X)
Besivance (besifloxacin hydrochloride)		other retinal disorders (362.X); cataract (366.X)
Byetta (exenatide)		diabetes type II (250.X0 and 250.X2)
Bystolic (nebivolol)		hypertension (401.X)
Chantix (varenicline)		current smoker (305.1); chronic airway obstruction (496)
Dexilant (dexlansoprazole)		disorders of esophagitis (530.X); disorders of stomach (536.X); gastric ulcer (531.X); peptic ulcer (533.X); syptoms involving the digestive system (787.X); abdominal pain (789.0X)
Durezol (difluprednate)		uveitis (364.00); cataract (366.X); other retinal disorders (362.X)

Continued

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
Effient (prasugrel hydrochloride)		angioplasty (V45.82, procedure codes 00.61-00.66); AMI (410.X); acute coronary syndrome (411.1); coronary atherosclerosis (414.0X)
Januvia (sitagliptin phosphate)		diabetes type II (250.X0 and 250.X2)
Levemir (insulin detemir)		diabetes (250.X)
Livalo (pitavastatin calcium)		disorders of lipoid metabolism (272.X)
Multaq (dronedarone hydrochloride)		atrial fibrillation and flutter (427.3X)
Nevanac (nepafenac)		cataract surgery (procedure codes 669.82, 669.83, 669.84); cataract (366.X); other retinal disorder (362.X)
Omnaris (ciclesonide)		seasonal allergy (477.X); sinusitis (461.X, 473.X); chronic airway obstruction not elsewhere classified (496.X); asthma (493.X)
Onglyza (saxagliptin hydrochloride)		diabetes type II (250.X0 and 250.X2)
Pradaxa (dabigatran etexilate mesylate)		atrial fibrillation or flutter (427.3X)
Pristiq (desvenlafaxine succinate)		major depressive disorder (296.X and 311); dysthymic disorder (300.4); schizophrenic disorders (295.X)

Continued

Technology	Procedure Codes	Eligible Diagnoses (ICD-9 Code)
Ranexa (ranolazine)		angina (413.X); coronary artery syndrom (411.1); coronary atherosclerosis (414.0X); heart failure (428.X); chest pain (786.5X); shortness of breath (786.05)
Rapaflo (silodosin)		prostatic hyperplasia (600.X); other disorders of urinary tract (599.X); symptoms involving urinary system (788.X)
Savella (milnacipran hydrochloride)		Back disorders (721.X, 722.X, 723.X, 724.X); rheumatoid arthritis (714.0); chronic pain (338.4, 338.29); osteoarthrosis (715.X); pain in joint (719.4X); other soft tissue disorders (729.X)
Nucynta (tapentadol hydrochloride)		pain (338.X, 780.96); diabetic neuropathy (250.6); joint pain (719.4); back pain (721.X, 722.X, 723.X, 724.X); osteoarthritis (715.X); abdominal pain (789.0X)
Tekturna (aliskiren hemifumarate)		hypertension (401.X)
Toviaz (fesoterodine fumarate)		functional disorders of bladder bladder (596.5X); retention of urine (788.2X), urinary incontinence (788.3X), frequency of urination (788.4X), urgency of urination (788.6X); other disorders of urethra and urinary tract (599.X)
Uloric (febuxostat)		gout (274.X)
Victoza (liraglutide recombinant)		diabetes type II (250.X0 and 250.X2)

each drug and service at the provider organization-level, developing a composite measure for utilization in each category, and fitting random effects models to composite measures to estimate the parameters of interest. In the first step, the following linear probability model was estimated for receipt of each drug and service by eligible beneficiaries:

$$Y_{ijp} = \beta_0 + \beta_1 X_i + \gamma_{jp}$$

where Y is equal to 1 if beneficiary i, attributed to provider organization p, had a claim for technology j, and 0 otherwise; X is a vector of individual characteristics, including age, sex, race and ethnicity, dual eligibility for Medicare and Medicaid, ERSD or disability as the original reason for Medicare, health status (represented by a count of the number of chronic conditions reported), and an indicator for whether the beneficiary died during the year; and γ_{jp} was a provider organization fixed effect. Of interest was γ_{jp}, which estimated the relative use of each new medical technology by physicians in organization p, after adjusting for the mix of beneficiaries attributed to the organization. This model was estimated separately for each of the 46 technologies using only the beneficiaries who were determined to be eligible for the technology (part of the denominator population). We then created a composite measure for relative use of new technologies in each category (i.e., Part A/B and Part D) and sub-category (i.e., imaging, radiotherapy, and physician-administered drugs), c, calculated as a weighted sum:

$$\widehat{R_{cp}} = \sum_{j=1}^{Jc} w_j \hat{\gamma}_{jp}$$

where w_j is the share of beneficiaries in the full sample qualifying for technology j and $\hat{\gamma}_{jp}$ was as estimated in the previous equation. For ease of interpretation we created linear combinations of the parameters from the fitted first-stage models to calculate the predicted use per 100 eligible beneficiaries in each category for each provider organization. To do this, we first averaged the predicted values, $\hat{y}_{ijp}$, for each provider organization. We then combined the averages of these

predicted values in each broad category using the same weights used to create provider organization-level composites. We used the mean of these estimates to center the distributions of use by provider organizations within each category of technology.

Next, a random effects model was fitted to the $\widehat{R_{cp}}$ values. Specifically:

$$\widehat{R_p} = \left(\widehat{R_{1p}}, \ldots, \widehat{R_{Cp}}\right)' \sim N\left(R_p, \mathrm{V_p}\right)$$

$$R_p = (R_{1p}, \ldots, R_{cp}) \sim N(\mu, \Sigma)$$

The main parameter of interest was Σ, because we were interested in the across provider organization variation in utilization and the correlation between the composite measures for each category of technologies within each provider organization. We estimated this from the data by calculating the sampling variance-covariance matrix, $\widehat{V_p}$, using methods described for analyzing data from the Consumer Assessment of Healthcare Providers and Systems (CAHPS) (Agency for Healthcare Research and Quality, 2015). Specifically, the elements of $\widehat{V_p}$ are the variances and covariances calculated as functions of the residuals for the models of beneficiary-level utilization for each technology j in category c:

$$\mathrm{Var}\left(\widehat{R_{cp}}\right) = \sum_i \left(\sum_{j=1}^{J_c} \frac{w_j}{n_{jp}} e_{ijp}\right)^2$$

$$\mathrm{Cov}(\widehat{R_{cp}}, \widehat{R_{c\prime p}}) = \sum_i \left(\sum_{j=1}^{J_c} \frac{w_j}{n_{jp}} e_{ijp}\right) \left(\sum_{j\prime=1}^{J_{\prime c\prime}} \frac{w_{j\prime}}{n_{j\prime p}} e_{ij\prime p}\right)$$

where n_{jp} was the number of beneficiaries eligible for technology j, in category c, assigned to provider organization p in 2011; w_j was the weight for technology j described earlier; e_{ijp} was the residual from the model fitted for use at the beneficiary level. We maximized the log likelihood using an expectation-maximization (EM) algorithm to obtain estimates of μ and Σ

with code developed by Hatfield and Zaslavsky (Hatfield & Zaslavsky, 2018). We normalized our results by dividing the standard deviation estimated in the Fay-Herriot model by the mean of the case-mix adjusted use for each provider organization's patients for each category (or sub-category) of technology.

RESULTS

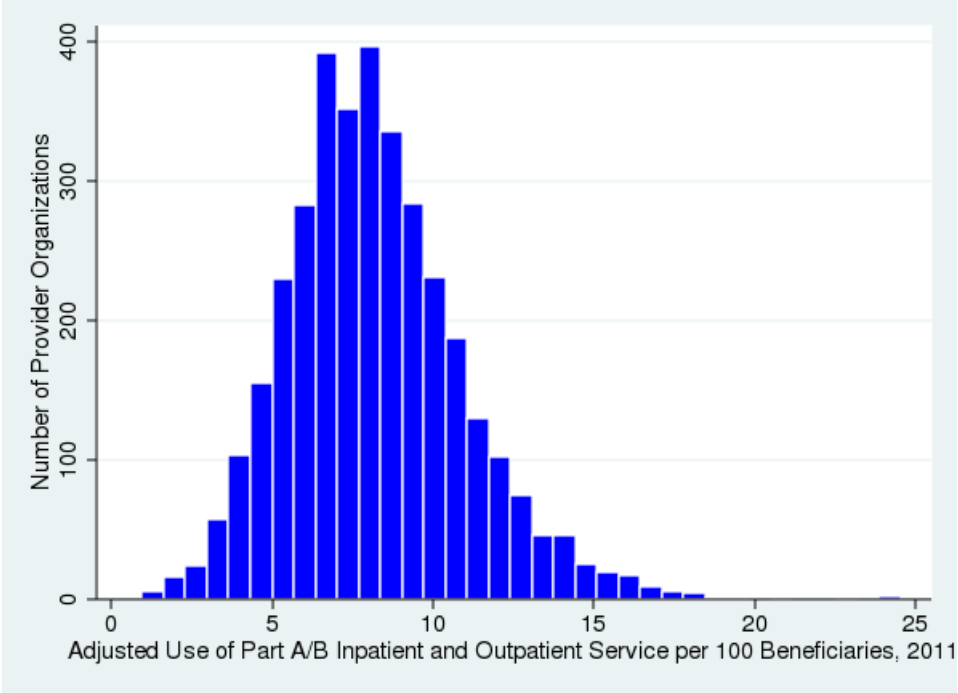
Our sample included 2,034,833 Medicare beneficiaries attributed to 3,546 provider organizations with a median of 388 beneficiaries in each organization. On average, before adjusting for beneficiary characteristics, 9 out of 100 eligible beneficiaries in each provider organization had a claim for a Part A and B covered technology and 12 out of 100 eligible beneficiaries in each provider organization had a claim for a Part D prescription drug on our list. Within the Part A and B sub-categories of imaging, radiotherapy, and physician-administered drugs, these rates were 5, 1, and 1 out of every 100 eligible beneficiaries in a provider organization, respectively. Table 1.2 presents a summary of beneficiary and provider organization characteristics.

Utilization of new technology varied between provider organizations. Figure 1.1 and Figure 1.2 show the distribution among provider organizations of the case mix-adjusted estimates for utilization in each broad category, as well as the sub-categories of Part A and B

Table 1.2: Summary of Beneficiary and Provider Organization Characteristics

	Full Sample	Any Claims for a New Technology	No Claims for a New Technology
Number of Beneficiaries	2,034,833	242,192	1,792,641
Average age	76.36	76.12	76.39
Male (%)	41	41	41
Race/Ethnicity (%)			
White	90	89	90
Black	7	7	7
Hispanic	1	1	1
Dual Eligible (%)	11	17	10
Average Chronic Condition Count	6.97	8.44	6.77
Disability/ESRD Medicare Reason (%)	9	12	8
End-Stage Renal Disease	1	1	1
Died in 2011	3	6	3
Claim for a New Technology (%)			
Any	12		
Part A/B inpatient/outpatient services	7	61	-
Part D prescription drugs	5	44	-
Imaging	5	39	-
Radiotherapy	1	8	-
Physician-administered drugs	1	7	-
Number of Provider Orgs.	3,546		
Average Beneficiaries Assigned to a Org.	388		
New Tech Use per 100 Elig Benes in Org.			
Non-Drug Services	8.64		
Prescription Drugs	12.05		
Imaging	4.84		
Radiotherapy	1.49		
Physician-administered drugs	0.83		

Figure 1.1: Distribution of Adjusted Rates of Part A/B Inpatient and Outpatient Services and Part D Prescription Drugs Use Among Provider Organizations in 2011



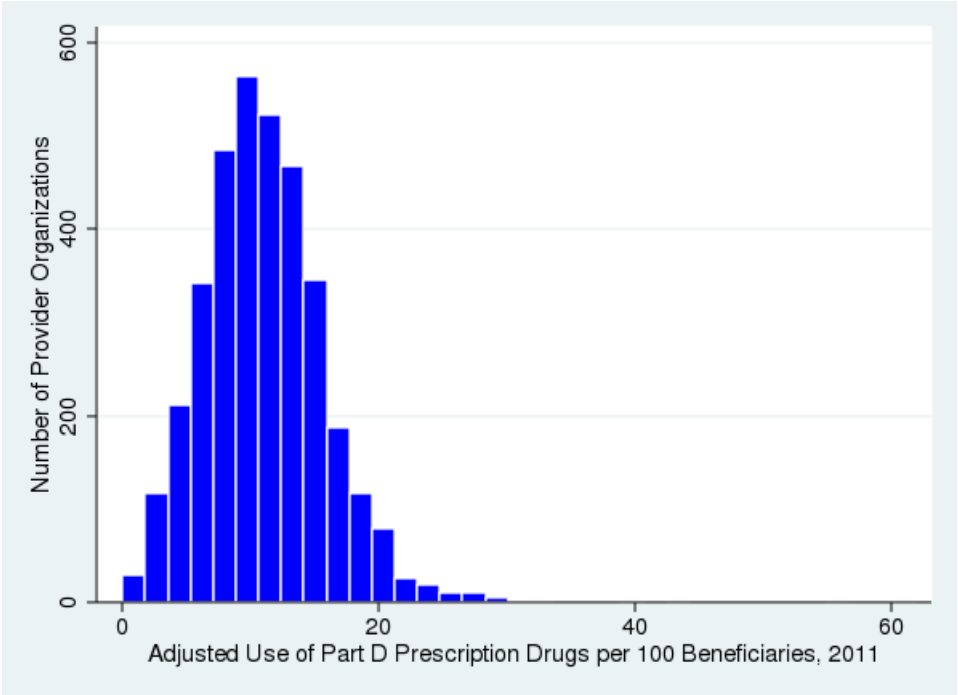
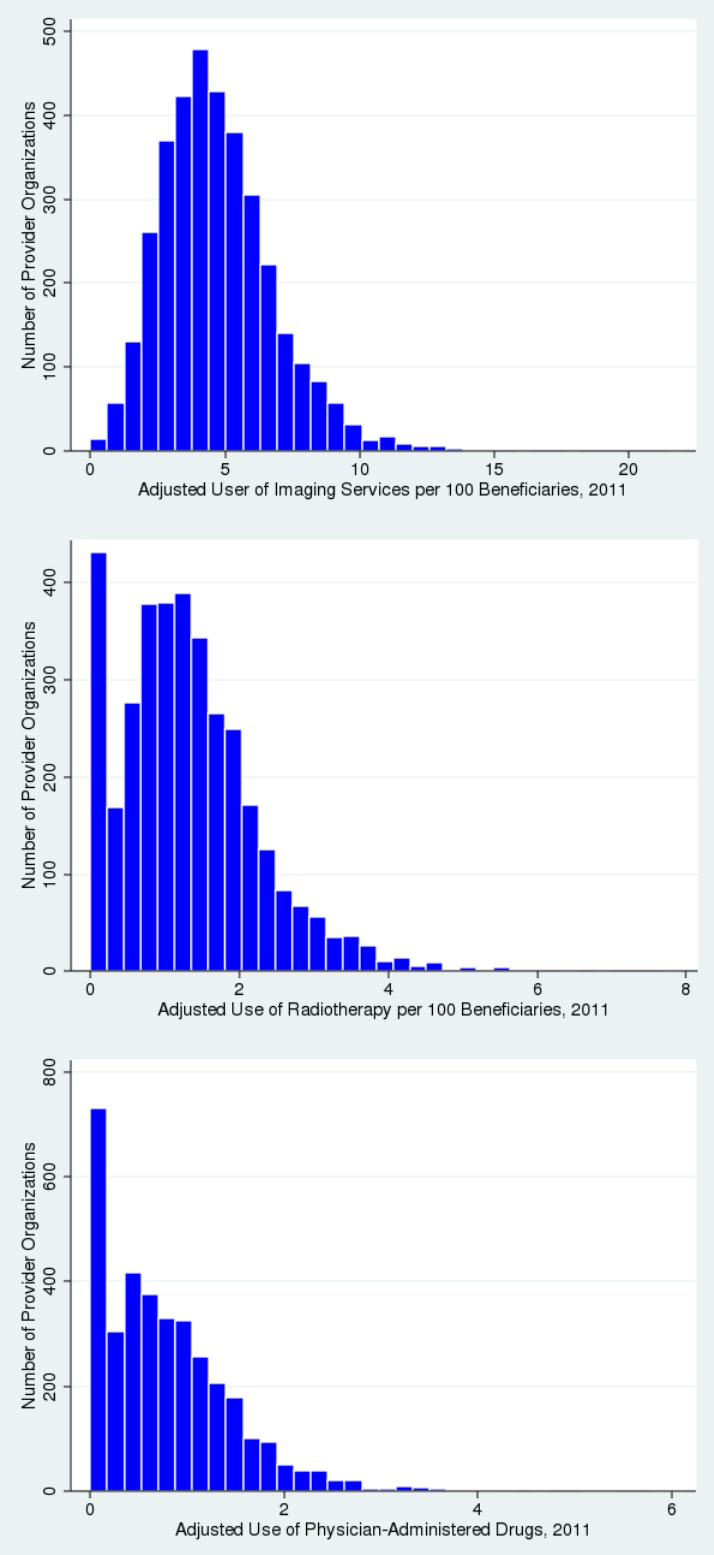


Figure 1.2: Distribution of Adjusted Rates of Use of Imaging, Radiotherapy, and Physician-Administered Drugs Among Provider Organizations in 2011



inpatient and outpatient services. These estimates are derived from the models for the provider organization-level composite use. The model adjusts for demographic characteristics and health status of the beneficiaries eligible for the service or drug, as well as the number of eligible beneficiaries in a provider organization. The adjustments for demographic characteristics and health status did not substantially change the provider organization-level variation in utilization for each category of technology. The standard deviation for use of new technologies across provider organizations was 2.0 per 100 eligible beneficiaries for Part A and B inpatient and outpatient services. For the subcategories it was 1.6 per 100 eligible beneficiaries for imaging, 0.5 per 100 eligible beneficiaries for radiotherapy, and 0.4 per 100 eligible beneficiaries for physician-administered drugs. Dividing these standard deviations by the mean adjusted use for the category yielded a normalized value of 0.24 for Part A and B services and 0.34, 0.38, and 0.50, for imaging, radiotherapy, and physician-administered drugs, respectively. The between-unit standard deviation for use of new Part D prescription drugs was 3.5 per 100 eligible beneficiaries. Divided by the mean adjusted use for Part D drugs this was 0.32.

There was little relationship within provider organizations in use of the two categories of new technology. Provider organizations that used new Part A and B inpatient and outpatient services for a larger share of their eligible patient population used slightly more new Part D prescription drugs. The correlation, however, was less than 0.1. Within the three Part A and B sub-categories, there was a stronger relationship between radiotherapy and imaging, as well as radiotherapy and physician-administered drugs, with correlations of 0.264 and 0.242, respectively. There was a very weak positive relationship between imaging and physician-administered drugs. Tables 1.3 and 1.4 presents the correlation coefficients for pairs of types of new technology.

Table 1.3: Correlation Between Use of New Part A/B Inpatient and Outpatient Services and Part D Prescription Drugs within Provider Organizations

Technology Category	Part A/B Inpatient and Outpatient Services	Part D Prescription Drugs
Part A/B Inpatient and Outpatient Services	1.0	
Part D Prescription Drugs	0.098	1.0

Table 1.4: Correlation Between Use of New Part A/B Sub-Categories (Imaging, Radiotherapy, and Physician-Administered Drugs) within Provider Organizations

Technology Category	Imaging	Radiotherapy	Physician-Administered Drugs
Imaging	1.0		
Radiotherapy	0.264	1.0	
Physician-Administered Drugs	0.055	0.242	1.0

DISCUSSION

We used hierarchical models to estimate utilization of 46 new medical technologies by medium and large provider organizations treating Medicare beneficiaries in 2011. We found variation across provider organizations within distinct categories of services and drugs. The relationships in use between pairs of categories of new medical technology ranged from no correlation within provider organizations for the use of broad categories of Medicare covered drugs and services to modestly positive correlations between radiotherapy and imaging and radiotherapy and physician-administered drugs. The variation across provider organizations could imply that organizations influence utilization of innovative medical care by affiliated

physicians. However, because we did not find consistent relationships across categories of new technology, we interpret the findings to imply that provider organizations do not exert broad and consistent influence over the utilization of innovative procedures, drugs, and practices. Instead, the influence of organizations likely depends on features of the particular technology, and may relate to the resources it requires, the disease areas in which it is used, and how it is reimbursed. Differences observed across provider organizations within categories of new technology are also likely influenced by the individual physicians practicing in those groups, as well as the specialists to which they refer, each of who exerts direct influence over the provision of different services or sets of services we examined. This supports a nuanced model of decision-making by providers relating to the integration of medical innovations into the health care system. In the context of payment reforms under which organizations bear risk, these findings suggest we are likely to see varied effects from these efforts on the adoption and use of new medical technology.

The variation across provider organizations within each category and sub-category of new technology could reflect differences in the degree to which organizations influence utilization. With respect to medical innovation, organizational decisions around investments in capacity to make certain new technologies more accessible or broadly available could encourage or discourage adoption and utilization. Organizations of different sizes likely vary in their involvement in these types of decisions. Provider organizations could also influence utilization through communications from management that direct physicians to the use of particular technologies and signal a general affinity or skepticism for using the most recent innovations. There also could be aspects of an organization's culture, such as how physicians interact and share information, which may or may not be supported formally by the organization, that catalyze or inhibit the diffusion of innovations. If provider organizations engage in these

decisions and activities in varying amounts, this could explain the range of rates of utilization that we estimate. If provider organizations were broadly inclined to influence utilization of new technology or possessed particular attributes that systematically encouraged or discouraged utilization of new innovations, we would expect to observe relationships within provider organizations across the distinct categories. In this study, however, these relationships are modest, suggesting that physicians affiliated with certain provider organizations are not systematically influenced to use or avoid new services and drugs across all types of innovative medical care. To the extent organizations do influence utilization of new medical technology, it appears to be limited to a subset of new services that require intense capital and labor resources. For example, both radiotherapy and imaging services require investments in equipment and specialized training. Our findings suggest that organizations making the capital and labor investments to support broad use of one of these types of services are also more likely to make similar investments with respect to the resources necessary for the other.

We interpret the findings from this study to suggest that smaller units, such as an individual physician or a subset of providers comprising a clinical care team, retain substantial influence over treatment decisions and the utilization of new technology in medium and large provider organizations. Prior work by the Institute of Medicine (IOM) is consistent with this interpretation. In that work, the authors found variation in utilization and spending existed at all levels and persisted as the unit examined got smaller (Newhouse et al., 2013). In this study, the persistence of heterogeneous utilization patterns across categories of new technology implies a nuanced model of clinical decision-making regarding the utilization of new technology. Provider organizations do not appear to be characterized by an underlying proclivity for the utilization new innovations. Rather, to the extent patterns of use existed at all, they were specific to a subset

of categories of new technology which shared similar patient populations and were in some cases complimentary services. Radiotherapy, imaging, and physician-administered drugs are largely used to treat cancer. These patterns were potentially influenced by the knowledge and experience of physicians in the organizations. The relatively modest correlations could reflect differences in the degree of specialization within the organizations or the extent of the networks of physicians involved in oncology care. Further work could examine sub-categories of technology used in other therapeutic or disease areas. It is possible that smaller units of providers can be characterized by their penchant for new technology.

Recent legislation has included provisions to encourage innovation and experimentation in the delivery and payment of care, with the goal of identifying effective strategies for lowering health care spending growth. Provider organizations are the focus of many of these efforts; for example, the Affordable Care Act created accountable care organizations (ACOs) in Medicare. Under these models, provider organizations are given targets for spending, and receive financial rewards if their attributed patients spend sufficiently less than the target in a year (Department of Health and Human Services, 2015). In some cases, organizations also bear the risk of spending more than the target and are responsible for a portion of the expenditures beyond a specified threshold (Department of Health and Human Services, 2018). Our findings suggest that provider organizations have variable influence over the utilization of new technology, and thus, we may expect new payment models that focus on provider organizations to have differing effects on the adoption of new innovations. This influence is likely to be stronger where the technology requires intense capital or labor investments, treats a patient population that is easy to define and identify, and is reimbursed separately each time it is used.

The expected impact of payment reforms on the utilization of new technology may depend also on how organizations are defined. Our analyses focused on medium and large provider organizations, defined as physicians who billed under a single TIN. Our findings could reflect differences in the latent networks of specialists to which these organizations refer or their attributed patients otherwise seek care. Organizations as we have defined them may appear to lack broad influence over the utilization of new technology because the decisions about use are being made by specialists who are not formally affiliated with the organization. In particular, the strength of the relationship between our provider organizations and the specialists that see the same patients may vary across provider organizations, as well as types of specialists. Work looking at correlations in the use of low-value services has found a stronger relationship when larger circles were drawn around groups of provider organizations, compared to examining individual TINs (Schwartz, Zaslavsky, Landon, Chernew, & McWilliams, 2016). Thus, there is reason to suspect that we may observe different patterns if we were to examine larger groups of provider organizations that work together.

Limitations

This study had several limitations. First, the analyses did not distinguish between new technology of higher and lower value. This research is a first step in understanding the utilization patterns of new technology, with the intention for future research to extend similar analyses to quality outcomes. Reducing the utilization of new technology is one way to limit spending growth. The effects on the value of care that result from reducing the adoption and use of new technology are ambiguous. Ultimately, we would like to see a reduction in the utilization of new technology that is of low value specifically.

Second, the data were cross-sectional. It used the level of utilization rather than the pace of uptake. It is possible that different provider organizations are at different places along the adoption curve at a point in time, even if they arrive at the same level of utilization eventually. The technologies were chosen to attempt to mitigate this concern. The drugs and services had broadly diffused, and thus are likely to be closer to the top of their respective diffusion curves.

Additionally, the set of new technologies did not represent the universe of medical innovations over the selected time period. They do represent a range of drugs and services used to screen, diagnose, and treat several different clinical conditions and include laboratory, radiology, and surgical procedures, as well as physician-administrated drugs and prescription drugs. They also have been validated by a physician panel that included doctors practicing across different specialties. So, while not comprehensive, they are a reasonable sample of new technologies.

Further, the sample consisted of claims data for beneficiaries in fee-for-service (FFS) Medicare. This posed two limitations. First, the generalizability of results to all Medicare beneficiaries and the broader population may be limited. Physicians may make different decisions about the adoption and use of new medical technologies for their population of FFS Medicare beneficiaries compared to other patients. Patients may also have differing demands for new technologies depending on their insurance coverage. Second, little clinical information was contained in these data and so we relied primarily on diagnoses to identify the set of eligible beneficiaries. It is possible that variation in utilization across provider organizations reflects sets of eligible beneficiaries in the denominator population for a particular technology that were not equally good candidates for that drug or service, rather than differences in the provider organization's proclivity for the new technology. We were not able to separate unmeasured

patient factors from physician decisions. If clinical factors were affecting the results, however, we would expect them to bias results toward stronger relationships between use of new technologies. Since we find weak relationships, this limitation is less concerning. It is also possible that certain providers only reported an eligible diagnosis on a claim when a particular service was delivered. Varying the definitions of the denominator populations would be a useful exercise to examine the sensitivity of the results to the definitions of eligible beneficiaries.

CONCLUSION

This study identified utilization of a broad range of innovative medical technologies in Medicare claims data, documented variation in utilization across provider organizations, and estimated correlations in utilization across these categories within provider organizations. We found substantial variation between provider organizations. The relationship in utilization across categories of technologies within provider organizations, however, was modest. These results suggest provider organizations do not broadly influence the utilization of all types of new medical technology. This implies that payment reforms focused on provider organizations will likely have different effects on the utilization of new technology depending on the type of medical innovation.

Chapter 2: Physician responses to a medical reversal and subsequent adoption of a new class of drugs – is the past prelude?

INTRODUCTION

Many pharmaceutical drugs are granted approval on the basis of limited or low-quality evidence and before the full range of the product's benefits and risks are known (Downing et al., 2014). Nevertheless, and despite typically high pricesv(Kesselheim et al., 2016), new drugs are often widely adopted. Evidence on the safety and effectiveness of a drug accrues as it is used in clinical care, and may lead to safety warnings being issued, but not until after the drug is already on the market (Downing et al., 2017). A medical reversal occurs when new evidence that a treatment is ineffective or unsafe emerges, calling into question its widespread use.

Most research examining medical reversals has focused on the affected drug or procedure and suggests that physicians change their treatment decisions in response to these information shocks (Bekelis, Skinner, Gottlieb, & Goodney, 2017; Dorsey, Rabbani, Gallagher, Conti, & Alexander, 2010; Howard et al., 2011; Howard & Shen, 2012; Smieliauskas, Lam, & Howard, 2014). However, whether physicians respond more broadly and change their prescribing of other drugs with uncertain benefits and risks is unknown. Physicians may respond to a medical reversal for one drug by adopting other new drugs more cautiously, limiting their use of new drugs until definitive evidence emerges. Thus, the extent of spillovers of practice-reversing evidence across drug classes has implications for drug developers and regulators. On the one hand, such spillovers could encourage developers to focus on drugs with a high probability of benefits and could encourage accelerated production of definitive evidence. On the other hand, spillover effects could stifle important innovation by discouraging the development of high-risk, high-reward drugs, the risks and benefits of which cannot be judged in advance.

In this study, we examined the relationship between physicians' responses to an information shock discouraging use of the oral hypoglycemic agent Avandia (rosiglitazone) and

their subsequent adoption of drugs in a new class, direct oral anticoagulants (DOACs). Like rosiglitazone, when DOACs were approved, there was not strong evidence that these new oral anticoagulants were superior to the existing treatment, warfarin (Connolly et al., 2009; Ezekowitz et al., 2007). Thus, by examining de-adoption behaviors at the physician level, we assess whether a major medical reversal had a spillover effect on the take-up of a subsequently approved drug class for which the risks and benefits were unknown.

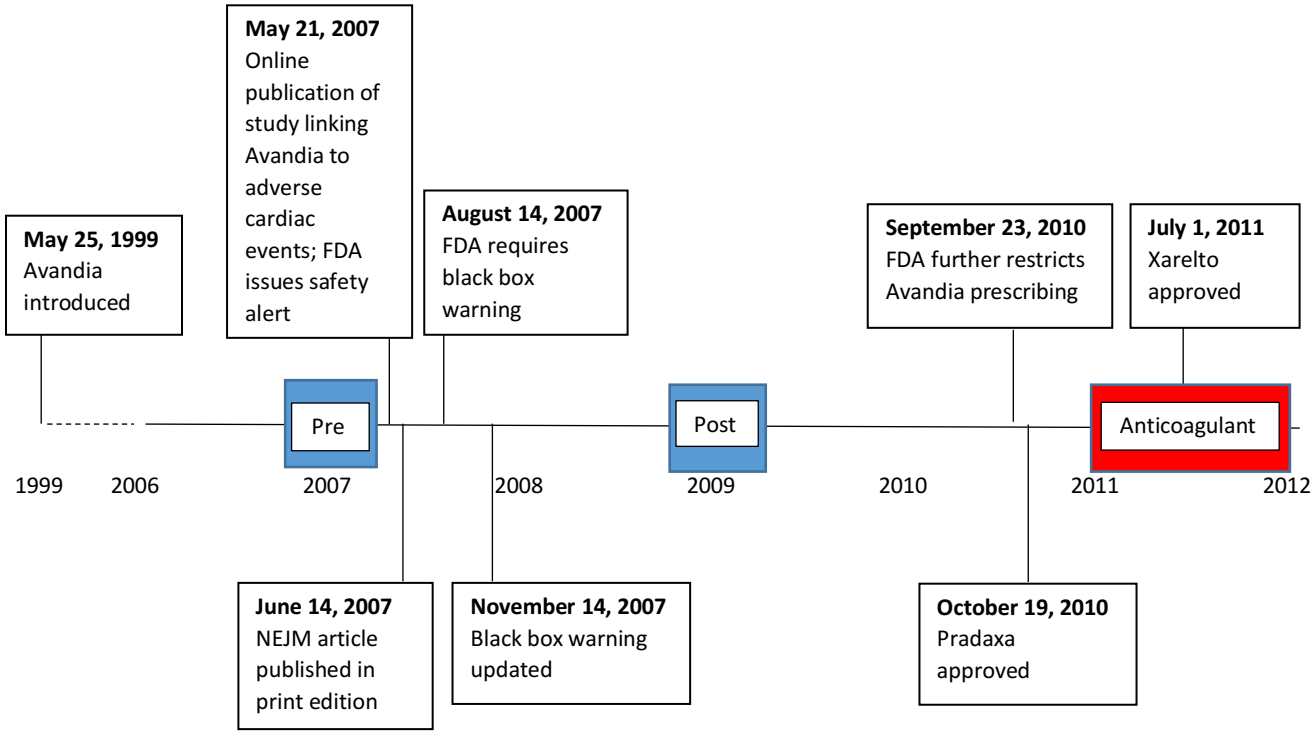
METHODS

Overview

In May 2007, evidence emerged of increased cardiovascular risk associated with rosiglitazone, one of two products in the thiazolidinedione (TZD) class of oral anti-diabetics (Nissen & Wolski, 2007). In response, the FDA immediately issued a safety alert (U.S. Food & Drug Administration, 2007), and all drugs in the class were required to carry a black box warning shortly thereafter (U.S. Food & Drug Administration, 2016). Figure 2.1 presents a timeline. Prior to this safety alert, the safety and efficacy of TZDs, especially compared to other existing antidiabetic drugs, was uncertain. We examined TZD prescribing before and after this safety alert and assessed whether changes in physicians' prescribing of TZDs were related to their subsequent prescribing of DOACs. We defined the pre-alert period as the four months immediately preceding the safety alert, January 2007 through April 2007. The post-alert period was the four months prior to the two-year anniversary of the safety alert, or January 2009 through April 2009, at which point the aggregate decline in TZD prescriptions had leveled off. We assessed use of two DOACs, Pradaxa and Xarelto, over the calendar year 2011, the first full

year drugs in this class were on the market and before evidence of their risks and benefits versus the existing treatment was available.

Figure 2.1 - Timeline



Data and Study Population

We analyzed prescription drug claims for a 20 percent random sample of Medicare beneficiaries using the Part D Drug Event (PDE) file. We included claims from 2007 through 2009 for fills of prescription drugs containing any of the 27 compounds and 7 types of insulin approved to treat type-II diabetes (see Table A2.1 in appendix 2 for full list), as well as all claims in 2011 for fills of one of three oral anticoagulants – warfarin, Pradaxa (dabigatran), and Xarelto (rivaroxaban). For each year, we attributed beneficiaries to the primary care physician (PCP) who prescribed the plurality of their diabetes drugs (or anticoagulants) in that year. PCPs included physicians with specialty codes for internal medicine, family medicine, general

practice, or gerontology. These specialties are most likely to treat patients with diabetes and to prescribe anticoagulants (Lo-Ciganic et al., 2016). Since our study examined the relationship between physicians' changes in TZD prescribing and their prescribing of DOACs in 2011, we identified PCPs with at least one filled prescription for a diabetes drug in the pre-alert and post-alert periods, and at least one filled prescription for an oral anticoagulant in 2011. The resulting study population included 69,697 unique prescribers.

Prescribing Outcomes

Using drug fill dates and number of days supplies, we created monthly indicators for whether a prescription covering the month was for the drug class of interest (TZD or DOAC, depending on the time period). We included all drugs in the TZD class, rather than just rosiglitazone, because we expected across-class spillovers to be greatest among physicians who abandoned TZDs entirely in response to the safety alert, rather than substituting other TZDs for rosiglitazone. All TZDs were required to carry the black box warning.

Patient Characteristics

We used information from the Medicare Beneficiary Summary File to determine age, sex, and whether disability or ESRD was the original reason for Medicare eligibility. We used the Chronic Condition Warehouse segment to assess the number of chronic conditions each beneficiary had accumulated through each year and determine diagnoses of cardiovascular chronic conditions specifically.

Statistical Analysis

We first modeled the probability of TZD prescribing (among all diabetes prescriptions) following the FDA safety alert for rosiglitazone. We fitted a multi-level regression model that had the following general form:

$$E[Y_{pijt}] = g(\beta_0 + \beta_1 post + \beta_2 X_{ijt} + b_{0j} + b_{1j} post)$$

where g(·) was a logit link function; Y was equal to 1 if the prescription p, for beneficiary i, written by physician j, covering month t was for a TZD; post indicated the post-alert period; X included individual- and physician-level characteristics. The random effects, b_{0j} and b_{1j}, reflect physician j's relative TZD proportion of diabetes prescriptions in the pre-alert and post-alert periods.

We next estimated the correlation between a physician's b_{0j} and b_{1j}. We were interested in determining whether physicians who prescribed relatively more TZDs before the safety alert prescribed relatively more TZDs after the safety alert. The multi-level structure was useful because it allowed us to estimate these relationships net of sampling error.

Finally, we assessed the relationship between the physician-specific effects (estimated in the first model) and use of DOACs. We modeled the probability of prescribing DOACs (dabigatran and rivaroxaban) versus warfarin (the conventional treatment) in each month of 2011. Our regression model had the following general form:

$$E[Y_{pijt}] = g(\alpha_0 + \alpha_1 X_{ijt} + \alpha_2 \hat{b}_{0j} + \alpha_3 \hat{b}_{1j})$$

where g(·) was a logit link function; Y was equal to one if the prescription p, for beneficiary i, written by physician j, covering month t was for a DOAC; X includes individual- and physician-level characteristics; $\hat{b}_{0j}$ was physician j's estimated pre-alert period TZD prescribing effect; $\hat{b}_{1j}$ was physician j's estimated post-alert period TZD prescribing effect. For ease of interpretability, we scaled $\hat{b}_{0j}$ and $\hat{b}_{1j}$ by the corresponding estimated across-physician standard deviation. The primary parameter of interest was the coefficient on the estimated physician-specific post-alert period effects, α_3, which quantifies the relationship between a physician's relative prescribing following the safety alert and her use of DOACs. Positive values meant that, conditional on use

in the pre-alert period, physicians with lower (higher) use following the safety alert were relatively less (more) likely to prescribe DOACs. This result would be consistent with spillovers across classes. That is, physicians who responded more strongly to the safety alert becoming more skeptical of a subsequently approved drug with uncertain risks and benefits. We included $\hat{b}_{0j}$ because the incremental response to the safety alert could be different for different starting points. We can thus think of $\hat{b}_{1j}$ as the response of physician j, relative to other physicians who had similar pre-alert period TZD prescribing. To account for potential correlation between anticoagulant prescriptions attributed to the same physician, standard errors were clustered at the physician level.

To account for case-mix differences between beneficiaries attributed to different physicians, we added beneficiary characteristics. We also added indicators for the state in which the physician practiced, effectively comparing prescribing practices of physicians within the same state.

Sensitivity Analyses

We conducted several sensitivity analyses. First, to address the possibility of floor effects from physicians who had very few patients on a TZD before the safety alert, we restricted the sample to the 10 percent of physicians who had the most TZD prescriptions in the pre-period (we also explore a less stringent restriction of requiring at least one TZD prescription in the pre-period). In a second sensitivity analysis, we fit the first set of models to rosiglitazone prescribing, rather than TZD prescribing. In a third sensitivity analysis, we included interactions between the chronic cardiovascular conditions and the post-alert period indicator. The safety alert suggested cardiovascular risk specifically, and thus may have a differential impact on treatment decisions for patients with these conditions. In our last sensitivity analysis, we fit the second set of models

to new oral anticoagulants in December of 2011, rather than over the entire year, as the physicians in our sample were rapidly taking up these drugs during this time.

Data preparation was conducted in using SAS, version 9.4 (SAS Institute), and analyses were performed using Stata, version 14 (StataCorp).

RESULTS

TZD Prescribing

Physicians responded to the safety alert for rosiglitazone by writing fewer TZD prescriptions. Figure 2.2 shows the number of prescriptions covering each month by type of TZD (there were two drugs in the TZD class on the market at the time: rosiglitazone and pioglitazone). On average, physicians were 48% less likely to prescribe a TZD in the post-alert period. The response varied by individual physician. Physicians with the strongest responses (top 10^{th} percentile) were 75% less likely to prescribe a TZD in the post-alert period, while physicians with the weakest responses (bottom 10^{th} percentile) were 15% more likely to prescribe a TZD. For physicians who were average TZD prescribers in the pre-alert period, that translates into a TZD share of 3% of all diabetes prescriptions for the strongest responders and a TZD share of 14% of all diabetes prescriptions for the weakest responders in April 2009. See Figure 2.3.

There were some differences between beneficiaries who did and did not have a TZD prescription in the pre-alert and post-alert periods. Beneficiaries with a TZD prescription were slightly younger on average (especially in the post-period), more often male, and had higher rates of hypertension and hyperlipidemia (see Table 2.1). When we controlled for beneficiary characteristics and physician state, the results did not meaningfully change. In the models incorporating beneficiary characteristics, older individuals, those who became eligible for

Medicare because of disability or end-stage renal disease (ERSD), and beneficiaries with any of the five chronic cardiovascular conditions included in our model were less likely to be on a TZD. Men and individuals with more chronic conditions were more likely to have a TZD prescription. The full results from the first stage are reported in Table 2.2.

Figure 2.2 – TZD Prescriptions as a Share of All Diabetes Prescriptions by Month

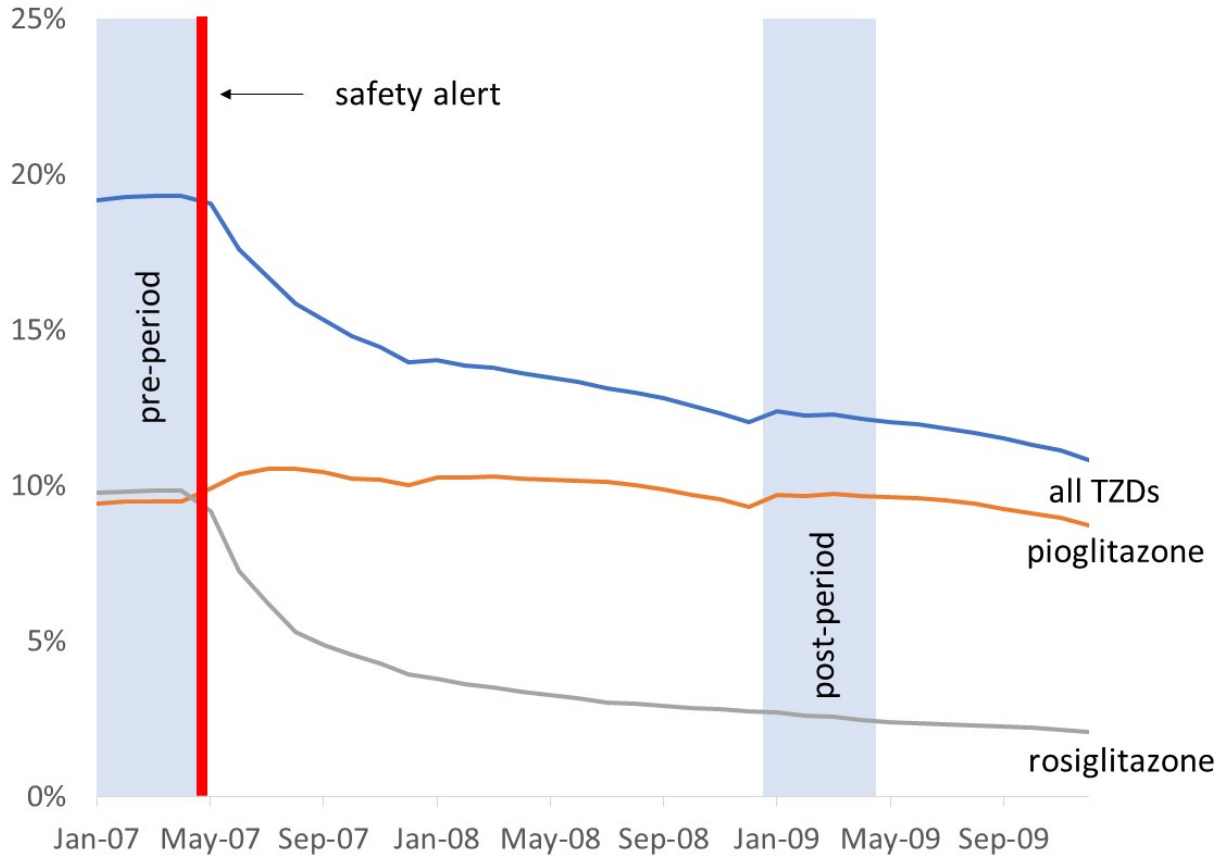
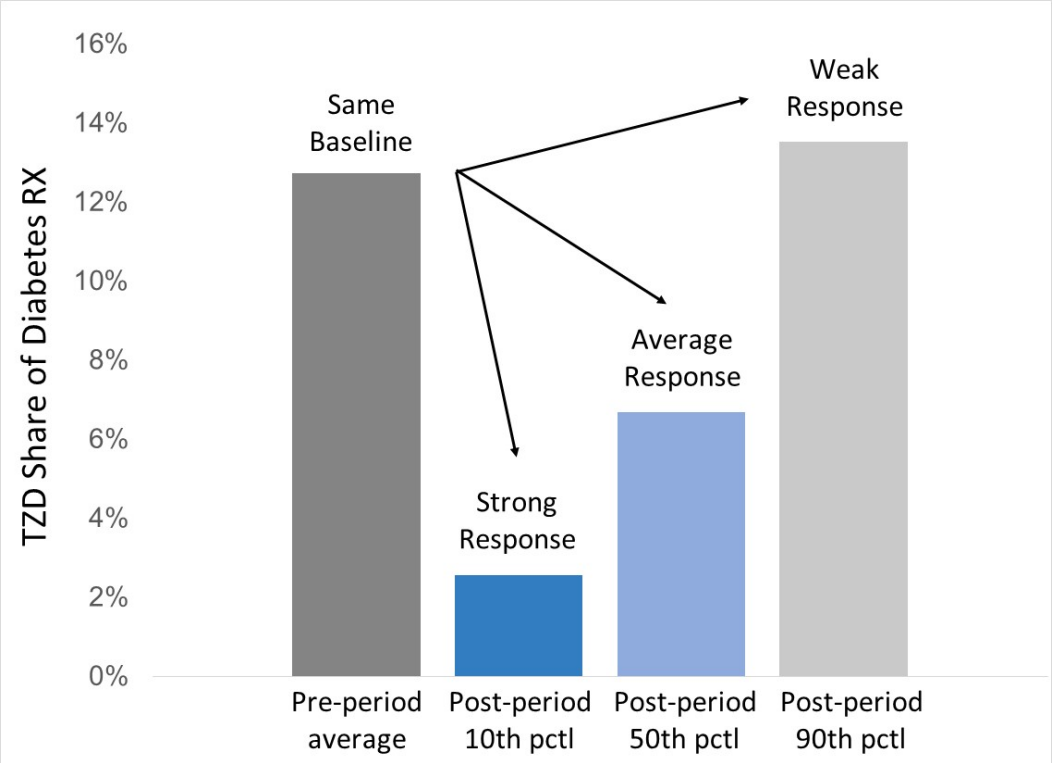


Figure 2.3 – Estimated TZD Prescriptions in April 2009 by Average Pre-Period Physicians at the 10th percentile, Median, and 90th percentile of Post-Period Prescribing



Note: Reflects estimated prescribing for physicians with median share of TZD prescriptions in April 2007, the month immediately preceding the safety alert, under model adjusted for beneficiary characteristics and physician state.

Table 2.1 – Characteristics of Medicare Part D Beneficiaries with a Prescription for a Diabetes Medication from a Primary Care Physician, by Study Period and TZD Status

	Pre-Period		**Post-Period**	
Characteristic	**TZD** (n=140,134)	**Non-TZD** (n=374,760)	**TZD** (n=106,927)	**Non-TZD** (n=496,835)
Age, mean	70.0	71.6	71.1	72.4
Male, %	42	40	45	41
Disability or ERSD Medicare, %	31	30	31	30
Chronic Condition Diagnoses, %				
Hypertension	82	77	80	77
Hyperlipidemia	76	67	76	71
Ischemic heart disease	51	50	47	50
Congestive heart failure	34	36	29	34
Stroke	15	17	14	16
Atrial fibrillation	10	13	9	13
AMI	5	6.	4	6

Table 2.2 – Odds Ratios for Factors Associated with TZD Prescribing from Multi-Level Mixed Effects Logistic Regression Models

	Odds Ratio (95% CI)		
TZD prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Post-Alert Period	0.53 (0.52 to 0.53)***	0.52 (0.51 to 0.53)***	0.53 (0.52 to 0.53)***
Patients with Diabetes Rx[a]	1.06 (1.06 to 1.07)***	1.07 (1.07 to 10.8)***	1.06 (1.05 to 1.07)***
Age		0.99 (0.99 to 0.99)***	0.99 (0.99 to 0.99)***
Male		1.09 (1.08 to 1.10)***	1.09 (1.08 to 1.10)***
Disability or ERSD Medicare		0.88 (0.86 to 0.89)***	0.88 (0.86 to 0.89)***
# Chronic Conditions		1.02 (1.02 to 1.02)***	1.02 (1.02 to 1.02)***
Hypertension		1.03 (1.01 to 1.05)***	1.03 (1.01 to 1.05)***
Hyperlipidemia		1.026 (1.24 to 1.28)***	1.026 (1.24 to 1.28)***
Ischemic Heart Disease		0.92 (0.91 to 0.93)***	0.92 (0.91 to 0.93)***
Congestive Heart Failure		0.85 (0.83 to 0.86)***	0.85 (0.84 to 0.86)***
Stroke		0.92 (0.90 to 0.93)***	0.92 (0.90 to 0.93)***
Atrial Fibrillation		0.80 (0.79 to 0.82)***	0.80 (0.79 to 0.82)***
AMI		0.81 (0.79 to 0.83)***	0.81 (0.79 to 0.83)***
State Fixed Effects	no	no	yes
Physician-Specific Effects			
Pre-period (std. dev.)	0.93	0.94	0.93
Post-period (std. dev.)	0.83	0.86	0.85
Pre- and post-period corr.	-0.19	-0.19	-0.20
PCPs, No.	69,697	69,618	68,984
Bene-month observations	6,121,681	5,617,706	5,540,841

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Correlation between Pre- and Post-Period Prescribing

Physicians who prescribed relatively more TZDs before the safety alert prescribed relatively fewer TZDs after the safety alert, but the negative correlation was modest. We found an almost identical relationship when we adjusted for beneficiary characteristics and physician state. The correlation between baseline level of TZD prescribing and response to the safety alert ranged from -0.19 to -0.20 in the three regression models.

DOAC Prescribing

There was no relationship between a physician's response to the safety alert and her DOAC prescribing. After controlling for beneficiary characteristics and state, we also found no relationship. However, physicians with higher levels of TZD prescribing in the pre-alert period had greater DOAC prescribing. Physicians with baseline TZD prescribing one standard deviation above average were between 9% and 14% more likely to prescribe DOACs in 2011. See Table 2.3 for full results.

Table 2.3 – Odds Ratios for Factors Associated with DOAC Prescribing in 2011 from Logistic Regression Models

	Odds Ratio (95% CI)		
DOAC prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Response to Alert	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)
Pre-Alert TZD Rx	1.14 (1.11 to 1.17)***	1.12 (1.09 to 1.14)***	1.09 (1.07 to 1.12)***
Patients with Anticoagulant Rx[a]	0.97 (0.96 to 0.99)***	0.97 (0.96 to 0.98)***	0.98 (0.97 to 0.99)***
Age		0.99 (0.99 to 1.00)***	1.00 (0.99 to 1.00)***
Male		1.04 (0.99 to 1.08)*	1.04 (1.00 to 1.08)*
Disability or ERSD Medicare		0.60 (0.56 to 0.64)***	0.59 (0.55 to 0.63)***
# Chronic Conditions		1.03 (1.03 to 1.04)***	1.03 (1.03 to 1.04)***
State Fixed Effects	no	no	yes
PCPs, No.	69,697	69,618	68,981
Obs	2,206,857	2,205,473	2,192,397

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Sensitivity Analyses

We had similar findings when we limited our sample to the 10 percent of physicians with the most beneficiary-months covered by a TZD in the first four months of 2007. These high-prescribing physicians responded to the safety alert by reducing their TZD prescribing and there

was no relationship between a physician's response to the safety alert and use of DOACs. The relationship between pre-alert and post-alert period TZD prescribing was also weak, but in the opposite direction: higher pre-alert period prescribers were higher post-alert period prescribers (see Table A2.2 in appendix 2). Our findings were also unaffected qualitatively when we modeled rosiglitazone prescribing instead of TZD prescribing in the first stage (see Table A2.3 in appendix 2), as well as when we included interactions between the presence of chronic cardiovascular conditions and the post-period (Table A2.4 in appendix 2). We also found no relationship between the response to the safety alert and use of DOACs in December 2011 rather than the full 2011 period (see Table A2.5 in appendix 2).

DISCUSSION

We found no difference in the use of DOACs based on how physicians responded to a safety-related information shock for oral antidiabetics in the TZD class. Our findings were robust to different model specifications, sample constructions, and variable definitions. These results suggest that the effects of a medical reversal for pharmaceutical products do not spill over to subsequently approved drugs in different therapeutic areas for which the evidence is also uncertain. These findings provide insight into how physicians form and change preferences for pharmaceutical products. They may also help inform the FDA's actions as the agency seeks to balance safety and risk considerations with access to innovative treatments.

Consistent with previous studies, we found that physicians responded to a safety-related information shock for rosiglitazone, but confined their response to the affected drug. Prescriptions for TZDs overall declined from 2007 to 2009, with prescriptions for rosiglitazone falling more precipitously than those for pioglitazone (the other drug in the TZD class) (Hampp,

Borders-Hemphill, Moeny, & Wysowski, 2014; Margolis et al., 2011; Shah et al., 2010). In addition, some physicians substituted to pioglitazone from rosiglitazone, even though the two are similar drugs and were both required to carry the black box warning (Hurren, Taylor, & Jaber, 2011). If this were to hold more generally, it suggests evidence can change physician behavior, but to do so broadly, nearly everything would have to be studied. Given resource and financial constraints, such an approach is likely infeasible, and so we may need to consider other ways to affect the general principles physicians incorporate into their practice.

We only examined the relationship between the response to the safety alert for TZDs and the subsequent use of DOACs. A possible reaction to our null finding is that physicians recognized the promise in DOACs (even though there was no evidence at the time to support this belief), and so used them anyway, and we may find spillovers for a less promising agent. The narrowness of the response to just rosiglitazone in the first stage, however, is informative. It suggests physicians do not extrapolate lessons from information shocks to other treatments (even those in the same class), and so it is unsurprising that we do not see broader spillovers into the use of new medications for a different disease.

Over the last decade, there have been several legislative actions affecting the authorities and resources available to the FDA for the approval and post-market monitoring of prescription drugs. Most recently, the 21st Century Cures Act encourages the expanded use of "drug development tools", such as biomarkers and surrogate endpoints, when the FDA approves new treatments (21st Century Cures Act, 2016). These provisions were aimed at improving access to innovative drugs, but have raised concerns as some worry they are compelling the FDA to laxer standards by expanding use of less reliable data. This concern arises, for example, because there are numerous examples of medical reversals for practices approved based on surrogate endpoints

(Prasad & Cifu, 2015). Our findings suggest physicians are unlikely to demand better evidence in advance of adopting new drugs, and so in this context, post-market monitoring and surveillance play a key role in protecting patient safety. Rigorous and accelerated evidence on how products perform in clinical settings will be critical in preventing overuse of new drugs with uncertain safety and efficacy profiles and unknown long-term effects.

A secondary finding of our study is that physicians who were relatively higher users of TZDs before the safety alert were also more likely to use DOACs. It is possible that patient characteristics drove this result. However, when we adjusted for physician case mix the results changed very little. Another explanation is that physicians possess varying proclivities for the use of novel over conventional treatments. Some physicians may be more inclined to adopt and use new drugs, even when there is no evidence of superior benefits or reduced risks.

Research examining health care cost growth has consistently concluded that innovations in medical technology drive health care spending growth over long periods of time (Chernew & Newhouse, 2012b). The relationship between use of different innovative treatments and the correlation between use of new treatments and spending trends at the physician level is unknown. Our findings suggest a possible promising area for future research examining whether certain physicians are systematically drawn to new therapies and services, while others are consistently slower to adopt novel technologies. This may be especially interesting to untangle given the weak relationship between a physician's baseline use of TZDs and their response to the safety alert. If some physicians have a greater avidity for new medical technologies and that avidity is unrelated to their responsiveness to evidence regarding the safety of the technology, it implies a limited role for evidence in incentivizing choice of high-value treatments under current conditions.

Other physician characteristics or behaviors may also explain the relationship between the use of TZDs in the pre-alert and post-alert periods and the use of DOACs. Physicians may vary in their ability to change prescribing patterns, with more agile physicians both adopting novel treatments and abandoning treatments for which safety concerns arise more intensely. If that were the case, we would expect to see physicians who responded more strongly to the rosiglitazone safety alert using more DOACs. We did not, however, observe such a relationship. In addition, there are likely differences in physician tolerance for risk related to potentially poor or dangerous outcomes associated with the use of a treatment. Given the typically weak evidence base at the time of approval, physicians who vary in their tolerance of uncertainty will have different adoption and utilization patterns of novel medications.

Limitations

Our study had several limitations. First, we were unable to account for unmeasured differences in the appropriateness of the novel drugs for patients attributed to different physicians. For example, patients may have different preferences which impact a physician's decision to substitute away from TZDs. These preferences may be correlated with patient characteristics we were able to measure, such as presence of a chronic cardiovascular condition. These patients may have had stronger preferences for switching away from TZDs because the safety alert was specific to risk of adverse cardiovascular events. After adjusting for presence of these conditions, as well as the interaction between these conditions and the post-period, there were trivial differences in our results. So, while it is possible that differences remained between physician patient populations that explain the observed treatment patterns, we do not expect such differences to change our findings.

Second, we had limited information about physicians. Ideally, we would have compared the prescribing of physicians similar on all observable characteristics. This would have allowed us to tease out whether there were characteristics, such as training or tenure, that explained prescribing, or if it was an unobservable attribute. Such a distinction would be useful for developing and evaluating the scope and appropriateness of policy interventions to encourage high-value innovation. Such information is not available in the data we used.

Additionally, our study is limited to physicians' responses to a single safety alert for Medicare Part D beneficiaries with prescriptions for two chronic conditions. We may also be interested in how physicians respond to new information regarding the efficacy of treatment and how the emergence of this type of information relates to future treatment decisions. Further, our findings may not be generalizable to treatments for acute conditions, or to treatment decisions for younger populations.

CONCLUSION

Using claims for prescriptions filled by Medicare Part D beneficiaries, we found no evidence that a physician's response to a safety-related information shock is related to prescribing of a subsequently approved drug for a different disease. These findings suggest that medical reversals do not have lasting dynamic effects on physicians' treatment decisions across therapeutic areas. This contributes to our understanding of physician preferences for medical innovations and how those preferences change over time and in response to information shocks. This may be useful as regulators consider post-market monitoring and surveillance activities and actions.

Chapter 3: Exploring an Instrumental Variable Approach to Identifying Physician Preferences for Medical Innovations

INTRODUCTION

Utilization of health care services and prescription drugs varies widely across geographic regions and at the clinical decision-making level (Newhouse et al., 2013). One reason for this variation is that physicians differ in their decisions to initiate, continue, or abandon treatments, even for similar patients. In particular, physicians have different preferences for innovative medical care. While differences in physician practice patterns have been examined (see, for example: Keating et al., 2018; Schwartz, Zaslavsky, Landon, Chernew, & McWilliams, 2016), the relationship between these differences and other outcomes of interest is unknown. Given the consensus that health care spending growth over long periods of time has been driven by the introduction and use of new medical innovations (Chernew & Newhouse, 2012a), it may be useful to know if physicians who demonstrate a proclivity for adopting new technologies also have higher spending growth.

Examining the relationship between a physician's practice patterns and the broader trends in the spending of their patients is complicated by the fact that many factors influence treatment decisions. Patient preferences pose a specific challenge because they are an input into physician decision-making and are also potentially correlated across types of services and treatments, as well as with outcomes, such as total spending. If patients systematically sort to physicians based on these preferences, which are also tough to measure, then it becomes difficult to disentangle patient demand factors from physician-level proclivity for medical innovation.

In this paper I examine addressing this challenge using an instrumental variable (IV) approach. This type of method has been used frequently in research on the effectiveness of prescription drugs, where concerns of unmeasured confounding are similar to the ones described above (Chen & Briesacher, 2011). A subset of this literature defines measures of physician preference for specific treatments that are plausibly unrelated to patient demand (Brookhart &

Schneeweiss, 2007; Schneeweiss, Setoguchi, Brookhart, Dormuth, & Wang, n.d.; Schneeweiss, Solomon, Wang, Rassen, & Brookhart, 2006). The key assumption is the proposed instrument is as good as randomly assigned. Thus, the selection of the sample of a physician's patients used to assign the IV values is a critical step. A primary objective of this paper is to present a set of descriptive analyses and empirical tests that define a framework for assessing the inclusion criteria used to select this sample and can be used to provide support for or against "randomness". I describe how to implement the proposed approach, including options to modify the sample restrictions. I then review the assumptions necessary for a valid instrument and present several tests to examine the sample definitions and assess the assumptions motivating the inclusion criteria. I conclude with a preliminary analysis of how the proposed instrument performs on 3 of these measures and the effects of altering the sample inclusion criteria in the context of prescription diabetes medications for patients receiving care from an endocrinologist.

PROPOSED INSTRUMENTAL VARIABLE APPROACH

I am interested in ascertaining a physician's penchant for novel treatments. One example of a novel treatment is the choice of a new class of drugs when writing a prescription. Often, physicians can choose from several medications, some of which have been available for decades, and others of which are relatively new. In many cases, there is little or no evidence that the novel treatment is superior to established therapies.[5] Ideally, I could observe the prescriptions filled by a physician's patients, compute the share of the prescriptions for new classes of drugs, and compare these shares across physicians, characterizing physicians on their relative use of novel drugs. These fills, however, to some extent, likely reflect patient preferences. Medicare patients,

[5] More generally, an IOM report found that half of all treatment decisions in the U.S. are not supported by evidence (Olsen, Grossmann, & Mcginnis, 2011)/

for example, are free to obtain care from nearly any physician. It is plausible that beneficiaries systematically sort to physicians in a way that is correlated with demand for certain drugs, confounding the influence of physician preferences on prescribing patterns. Further, patient-level preferences are not easily observable, particularly in claims data, and so are difficult to fully account for in a model of physician prescribing. Thus, what looks like a physician's penchant for novel drugs could reflect differences that stem from beneficiaries.

To address the bias introduced by omitting beneficiary preferences, I examine using prescriptions filled by a specialist's new patients. When a beneficiary first sees a specialist, it is often a result of a referral from a primary care physician. These referrals are plausibly random, driven by wait times or distance, rather than reflective of patient preferences for physicians with particular practice patterns. Variation in the prescriptions filled following these visits may then be attributed to differences in physician preferences and can be used to characterize physicians based on their use of novel drugs.

There are several ways to define an instrumental variable that characterizes a physician's prescribing of novel drugs for new patients. I assess a dichotomous variable, equal to 1 if any of the physician's new patients fill a prescription for a drug in a novel class following their first visit, and 0 otherwise. An alternative option is a continuous variable calculated as the share of new patients who fill a prescription for a drug in a novel class following their first visit. As a third option, the most recent prescription a new patient fills could be used to define a dichotomous variable equal to 1 if the fill is for a drug in a novel class, and 0 otherwise.

Additionally, the set of potential treatment options needs to be defined. The proposed IV characterizes physicians based on their choice of a novel drug. It is not always possible in health care claims data to confirm a prescription was written by the same physician with which the patient had a recent visit. To increase our confidence that fills for a prescription reflect the

treatment decision of the physicians included in our sample, we can require that the prescription is filled within a specified timeframe following the specialist visit. Additionally, we can restrict to fills for a drug that the patient did not have any fills for before the specialist visit. This way we ensure we are not attributing decisions of previous physicians to the specialist. Alternatively, we can limit to patients who had no prior medications.

Implementation considerations

The first step in implementing the IV approach is to select the sample of treatment decisions used to assign the IV values. There are two levels of inclusion criteria to define: 1) included physicians and 2) eligible patients. In the ideal choice set, beneficiaries are distributed among physicians without respect to their individual preferences over the treatment options. Thus, the criteria are selected to address sources of patient sorting to physicians based on their preferences. A subset of the inclusion criteria can be modified to obtain a sample that more plausibly satisfies the requirement of randomness depending on the analyses and tests discussed in the next section.

Included physicians

We are concerned that patients sort to physicians based on their preferences for treatment. This can be addressed by restricting the sample based on characteristics of physicians and their practice environments that are likely associated with treatment preferences of beneficiaries. Two such characteristics include the physician's specialty and their relationship with referring physicians.

It is plausible that patients randomly choose a physician within a specialty, even if their choice of specialty is not random. Many health conditions can be treated by physicians with different specialties and it may be easier to obtain information about the practice patterns of a certain type of doctor than it is an individual physician. A patient's choice of type of doctor may

then be related to their treatment preferences. For example, patients with more advanced or complicated conditions may be both more likely to see a specialist and more willing to try novel treatments. The IV I examine uses prescribing of specialists to address this potential sorting.

Primary care physicians have a finite set of specialists to which they can refer patients. For a referral to be random, the patients of the referring physician must have new visits with multiple specialists, at least in areas where multiple specialists are available. Otherwise, the specialist a patient sees is determined solely by where they obtain primary care services, and we would be worried that beneficiary preferences influencing choice of a PCP transmit to specialists. The instrument examined here limits to specialists from which the new patients' PCPs refer to at least two specialists. This restriction can be modified by increasing the number of specialists to whom the PCP refers, setting requirements for the distribution of referrals from the PCP, or by removing the restriction altogether. Alternatively, we can restrict to specialists whose new patients were referred by at least two different PCPs. We can also impose this restriction at the provider organization level (defined by the tax identification number under which PCPs bill).

Eligible patients

To further address the concern of patient sorting based on treatment preferences we can apply restrictions to the set of patients we include in the sample. The primary restriction imposed in this paper is limiting the sample to new visits, and specifically, the first new visit a patient has to any specialist for an included diagnosis. This excludes individuals that may be "shopping" around for a specialist, as well as established patients that may have seen other specialists before settling on their current physician. In addition, patients who previously filled a prescription for a novel treatment are excluded. A physician's decision to continue or abandon novel treatments for these individuals are likely affected by the patient's experiences and preferences with the

treatment, rather than reflective of the physician's penchant for medical innovations. Additional restrictions could include narrowly defining the diagnoses that identify eligible visits, including only new visits that occur within a specified period after a reference visit with a PCP, and limiting to visits where the patient traveled less than a certain number of miles. I discuss each of these additional restrictions in detail below.

An individual's reason for seeing a specialist is potentially correlated with the treatment they hope to receive and may affect the physician to which they are referred or choose to seek care. Conceptually, we may want to select patients with conditions of similar severity or level of complication. While this has the benefit of better matching patients to suitable treatments, it could limit the scope of outcomes to which the IV could be applied. The extent to which diagnosis is correlated with non-random sorting of patients to physicians may vary across conditions and be more relevant in some circumstances. The sensitivity of the IV assignment to the definition of eligible patients can be examined, as discussed in the next section.

A new patient to a specialist could reflect either a referral from a primary care physician or a self-referral. Individuals choosing to go directly to a specialist could differ in relevant ways from those that are referred by a PCP. To select only new visits resulting from a referral, we can limit the sample to new visits that were preceded by a visit with a PCP within a specified timeframe. The "lookback" window could vary, say from one week to three months.

The last type of restriction I consider is distance between the patient and the specialist. One reason patients may choose a physician is convenience associated with minimizing the travel time from their home to the physician's office. We are not concerned about sorting along this dimension (as long as we control for other things like health status that could influence treatment and how far a patient is able/willing to travel). Thus, we can limit the sample to patients who travel no more than a specified number of miles for their first visit with a specialist.

Alternatively, we can create a relative measure of distance that looks at how much further a patient traveled than their closest specialist. We can limit to patients who traveled no more than a certain number of miles, or a proportion of the shortest travel distance available.

IV assumptions

For a causal effect to be identified using an instrumental variable approach, two assumptions must be met. First, the instrument must be related to the treatment. In my context, this means that physicians characterized as higher users of novel drugs for new patients (the randomly assigned population), must have greater use of the novel drugs in their broader established patient population (who may systematically sort to physicians based on unobservable characteristics).

The second assumption is the instrument can only be related to outcomes of interest through its relationship with the treatment. This means the assignment of the instrument is random, conditional on covariates that can be accounted for in the model, and has no direct effect itself on outcomes. This is commonly referred to as the "Exclusion Restriction."

Tests of assumptions

Before implementing an instrumental variable approach, it is important to demonstrate the instrument of choice satisfies the necessary assumptions. Below I outline several tests and discuss the motivation behind each. I briefly discuss how to verify the first assumption. The focus of this section is on the exclusion restriction. It is not possible to directly verify this assumption holds. Instead, the researcher must make an argument. The framework presented below is intended to serve as a set of tools to provide support for or against such an argument.

Assumption 1: Instrument is related to the treatment

A straightforward way to empirically test whether the instrument is related to the treatment is to regress the treatment on the instrument. Specifically, estimate the following model:

$$Y_{ip} = \alpha + \beta X_i + \gamma IV_p$$

where, Y_{ip} is equal to 1 if an established patient of physician p receives the novel drug; X_i is a vector of beneficiary characteristics; and IV_p is the assigned value for the instrumental variable characterizing physician p's use of the novel drugs for new patients. The coefficient on the IV, γ, is the parameter of interest in this model. For the instrument to satisfy this first assumption, the coefficient should be positive and statistically significant. The interpretation of γ will depend on how the IV is defined – whether it is a continuous or dichotomous variable. The model should include any covariates that are known or suspected to affect the prescribing decisions of physicians. These potentially include beneficiary demographics, comorbid conditions, overall health status, other current prescriptions, the Part D plan in which a beneficiary is enrolled, and where the beneficiary obtains primary care services. It could also include information on the practice environment in which the physician operates. Given the documented variation across geographic regions, it may also include indicators for hospital referral regions, or other geographic units. In these models, standard errors should be clustered at the physician level.

Assumption 2: Exclusion restriction

This assumption is impossible to verify directly and instead the researcher should present evidence that rules out violations to the extent possible. If we think through other patterns in the data we should expect to see if the requirement of random assignment is satisfied, we can develop empirical tests. Individually, these may not be sufficiently convincing, but taken together, they bolster the case that the exclusion restriction is met. These tests can be applied to

samples defined using different inclusion criteria to evaluate whether imposing or modifying the sample restrictions is justified in the particular context.

1. *Compare beneficiary characteristics.* The exclusion restriction implies that new patients to different specialists should not vary on observable characteristics. At the very least, we would like to observe smaller differences than we do for the established patients. This can be examined by looking at the characteristics of new and established patients for physicians who are assigned the treatment versus the physicians who are not assigned the treatment. This is less than satisfying because we can control for these observable characteristics in our model, and likely will. However, if we see that the IV does nothing to attenuate differences in the patient populations on observable characteristics, we would have even more reason to be concerned about the unobservable characteristics (for which we cannot control in our models).
2. *Model patient RxHCC score.* A second way to verify that patients do not systematically differ across physicians is to predict the patient's RxHCC score as a function of the physician they visit as a new patient. RxHCC is the Centers for Medicare and Medicaid's hierarchical condition category risk-adjustment model used to determine payments to Medicare Advantage and standalone prescription drug programs under Medicare Part D. It is a more robust measure of beneficiary characteristics that affect utilization and spending on prescription drugs that includes demographics and diagnosis information. RxHCC also incorporates previous prescription drug utilization and spending, so may capture aspects of the patient's preferences that are more difficult to observe. Empirically, we can incorporate fixed effects for each physician and then test that the variance in the estimated values from

the fitted model is small. If the new patients sort randomly to specialists, then we would not expect the physician-specific parameters from the model of RxHCC score to differ across physicians.

3. *Examine distribution of measures of health status.* Health care claims data contain limited information relating to the severity or complexity of a patient's condition. It is possible, however, to examine the specific diagnoses listed on the new visit with the specialist. These diagnoses can provide information about whether patients with more advanced, complex, or difficult-to-treat diseases sort to specialists in a non-random way. For example, individuals with a variety of cardiovascular conditions may seek care from a specialist. We can test empirically if certain specialists are more likely to see new patients with particular conditions and how that relates to other characteristics of their patient population and treatment decisions. We can also observe the prescriptions for medications a beneficiary filled prior to visiting the specialist. For certain conditions, this may give an indication of the progression of the disease or information about beneficiary preferences related to treatment.

PRELIMINARY ANALYSIS

Overview

The number of medicines available to treat diabetes has expanded in recent years. Since 2005, nearly three dozen new medications have been approved by the U.S. Food and Drug Administration (United States Food and Drug Administration, 2018). These include new classes of drugs, injectable biologics mimicking natural hormones, new insulins, and combination products of previously approved and available compounds. This wave of innovation began with the approval of Byetta (exenatide) in April 2005, the first drug in the glucagon-like peptide-1

(GLP-1) receptor agonist class. In October 2006, Januvia (sitagliptin phosphate), the first dipeptidyl peptidase-4 (DPP-4) inhibitor, was approved. Over the next five years, approvals followed for two additional DPP-4 inhibitors, Onglyza (saxagliptin hydrochloride) and Tradjenta (linagliptin), an additional GLP-1 receptor agonist, Victoza (liraglutide), combinations of these compounds and metformin, as well as extended release versions of these products. Below, I characterize endocrinologists based on their prescribing of these two novel classes of drugs for new patients. I present preliminary analysis examining how the instrument performs on three of the measures discussed above and explore the effects of two modifications of the inclusion criteria.

Data and Sample

I use claims data for a 20 percent random sample of Medicare beneficiaries in 2011. The sample includes endocrinologists who treat Medicare beneficiaries with diabetes identified using the provider specialty, diagnosis, and HCPCS codes on the carrier line claims. These visits are classified as a new patient visit (HCPCS codes 99201 – 99205) or an established patient visit (HCPCS codes 99211 – 99215) and are determined to be for diabetes if they contained one of the following ICD-9 diagnosis codes: 250.XX (diabetes mellitus), 357.2 (polyneuropathy in diabetes), 362.0X (diabetic retinopathy), V45.85 (insulin pump status), V53.91 (fitting/adjustment of insulin pump, insulin pump titration), V65.46 (encounter for insulin pump training), 996.57 (mechanical complications, due to insulin pump).[6] I restrict to beneficiaries who can be attributed to a primary care physician for most of their primary care services and have a new visit to an endocrinologist (excluding new patient visits for beneficiaries that have previous visits with a different endocrinologist). Further, I exclude new patients who filled a

[6] This list of diagnoses was taken from the Health Care Cost Institute's 2016 Health Care Cost and Utilization Report.

prescription for a novel diabetes drug prior to their first visit with an endocrinologist. Only endocrinologists that had claims for visits for both new and established patients over 2010 and 2011 are included. The sample is limited to endocrinologists whose new patients' PCPs refer to at least two different endocrinologists during the period. Endocrinologist prescribing is examined for the subset of beneficiaries enrolled in Part D drug coverage for the full year in which their office visit occurred. The Medicare Part D Drug Event File (PDE) was used to identify fills for prescriptions for diabetes medications, including insulin, in 2010 and 2011.

I explore two types of modifications to the sample definition. First, I limit to beneficiaries who have a claim with a diabetes related diagnosis with a PCP within one month of their new visit to an endocrinologist. Second, I restrict to new patients that have no history of insulin prescriptions prior to their first visit with an endocrinologist.

Instrumental Variable Assignment

To implement this approach, I identify fills for prescriptions for diabetes drugs that occurred within seven days of a beneficiary's first visit as a new patient to an endocrinologist. I identified fills for drugs that belong to one of the novel classes (GLP-1 receptor agonist and DPP-4 inhibitors). In each year, physicians were assigned a value of 1 if they had at least one patient who filled a prescription for a drug in one of the novel classes in that year and 0 otherwise.

Treatment Definition and Analysis Sample

Endocrinologists' assigned IV values are used to predict whether their established patients receive a prescription for a drug in a novel class. The set of established patients includes beneficiaries with a claim for an established patient visit and no new patient visits during the study period. Since beneficiaries sometimes saw more than one endocrinologist, they were attributed to the physician who billed for the most visits (and in the event of a tie, the physician

who billed for the largest amount of charges). I examine prescriptions each beneficiary filled in 2010 and 2011 and define an indicator variable equal to one if an established patient has a fill for a drug in a novel class and zero otherwise.

Results

The sample included 834 endocrinologists who saw a total of 1,927 new diabetes patients meeting the inclusion criteria over 2010 and 2011. Of these physicians, 63 had at least one new patient fill a prescription for a novel diabetes drug in 2010 and 78 had at least one new patient fill a prescription for a novel diabetes drug in 2011. These same endocrinologists saw 3,221 established patients over 2010 and 2011. On average, 26% of a physician's established patients filled a prescription for a novel diabetes drug. Those who had at least one new patient fill a prescription for a novel diabetes drug had a higher share of established patients with prescriptions for these drugs. This difference is larger in 2011. See Table 3.1 for a summary of the sample after imposing two additional criteria – limiting to new patients who had a visit with a PCP within 30 days of their first visit to an endocrinologist and limiting to new patients with no previous history of insulin use.

Table 3.1 Summary of Sample Characteristics, by Sample Criteria

Sample Characteristics	Baseline Sample	Restrict to New Patients with PCP visit w/in 30 Days	Restrict to New Patients w/ no Prior Insulin Rx
Endocrinologists, No.	834	435	211
New Patients, No.	1,927	624	259
At Least One New Patient w/ Rx for Novel Drug, No.			
2010	63	13	7
2011	78	21	13
Established Patients, No.	3,221	1,940	1,813
Share w/ Rx for novel drug, %	26.0	26.5	29.1
2010: IV assignment=0	25.3	26.1	33.3
2010: IV assignment=1	28.4	28.3	27.8
2011: IV assignment=0	25.5	26.4	29.0
2011: IV assignment=1	33.9	33.6	34.1

*IV assignment is based off prescriptions for the endocrinologist's new patients in the same year.

Assumption 1

The relationship between the instrument and the treatment is strong and statistically significant in 2010 and 2011 for the baseline sample. After controlling for demographic characteristics, several measures of health status, and state of residence, beneficiaries attributed to physicians who prescribed a novel diabetes drug to a new patient were more likely to fill a prescription for a GLP-1 receptor agonist or DPP-4 inhibitor in 2010 and 2011. These established patients had a probability of filling a prescription for a novel diabetes drug that was 7% and 11% higher, on average, in 2010 and 2011, respectively. The relationship is stronger in 2010 after restricting the sample used to assign the IV value to new patients who had a visit to a PCP within 30 days of their first visit to an endocrinologist. It is also strong in 2010 after restricting this sample to new patients with no prior insulin prescriptions in the Part D claims. For 2011, imposing the additional sample restrictions weakens the relationship and it is no longer statistically significant. See Table 3.2 for full results.

Table 3.2 Coefficient on IV Assignment from Linear Probability Model of Filling a Prescription for a Novel Diabetes Drug for an Endocrinologists Establish Patients Under Varying Sample Definitions

	Coefficient on IV Assignment	
Sample	**2010**	**2011**
Baseline Sample	0.07 (0.1 to 0.12)**	0.11 (0.05 to 0.16)***
Restrict to New Patients with PCP visit w/in 30 Days	0.17 (0.08 to 0.26)***	0.09 (-0.03 to 0.21)
Restrict to New Patients w/ no Prior Insulin Rx	0.16 (0.07 to 0.25)***	0.04 (-0.10 to 0.18)

* p<0.10
** p<0.05
***p<0.01

Assumption 2

To examine support for the exclusion restriction, I compared the characteristics of new and established patients and examined the distribution of prescriptions filled prior to new patients' first visit with an endocrinologist.

Comparison of beneficiary characteristics

The instrumental variable does only a fair job of attenuating differences between patients of endocrinologists by the assigned value of the instrument. Overall, the samples look more similar for new patients visiting an endocrinologist assigned an IV value of 1 versus 0 on approximately half the characteristics examined. Further, the improvement is inconsistent across years and sample definitions. For example, there is a smaller difference in the average age of patients across two of the sample definitions for new visits in 2010, while the opposite is true for 2011. Similarly, the IV improves (or makes no worse) the difference in average number of chronic conditions in 2010 across the baseline sample and two alternatives, but increases the spread in two of the three samples in 2011. See Table 3.3 for full summary.

Examination of Prescriptions Filled Prior to New Visit with Endocrinologist

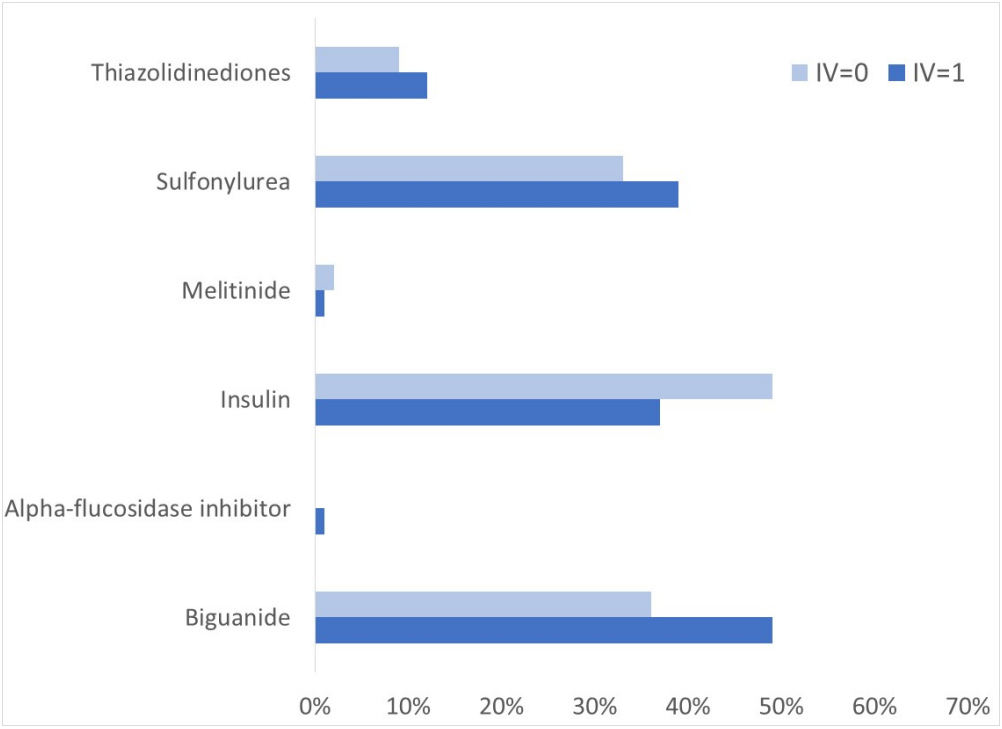
There are differences across all sample definitions in the share of new patients with a prior prescription for each class of diabetes drugs. These differences do get smaller as the sample definitions change. In the baseline sample, more new patients with visits to an endocrinologist with an assigned IV value of 1 have prescriptions for a biguanide (metformin), sulfonylurea, or TZD. These differences narrow substantially when the 30 day limit between PCP and endocrinologist visit is included. It reverses slightly for TZDs and biguanides when examining the sample of new patients who had no previous insulin prescriptions. See Figure 3.1. (See Table A3.1 in appendix 3 for numbers underlying figure.)

Table 3.3 Summary of Characteristics of Established and New Patients, by IV Assignment

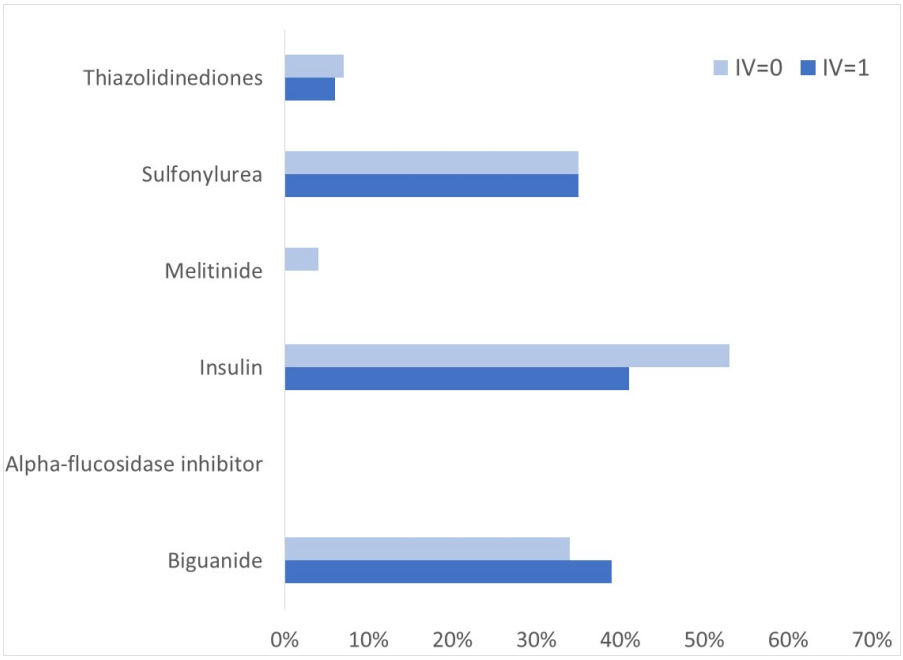
	2010				2011			
	Established Patients		New Patients		Established Patients		New Patients	
	Baseline Sample							
Characteristics	**IV=1**	**IV=0**	**IV=1**	**IV=0**	**IV=1**	**IV=0**	**IV=1**	**IV=0**
Age	69.9	68.5	68.5	67.2	69.8	69.5	69.0	67.7
# Chronic Conditions	9.6	9.1	9.3	8.9	10.1	9.7	9.4	9.1
Male	0.4	0.4	0.5	0.4	0.3	0.4	0.4	0.4
White	0.7	0.7	0.8	0.7	0.8	0.7	0.8	0.7
Black	0.1	0.2	0.1	0.2	0.1	0.2	0.1	0.2
Hispanic	0.1	0.1	0.1	0.1	0.1	0.1	0.0	0.1
Disability or ESRD Medicare	0.3	0.4	0.4	0.4	0.3	0.4	0.3	0.4
AMI	0.1	0.1	0.1	0.1	0.1	0.1	0.1	0.1
Congestive Heart Failure	0.4	0.5	0.4	0.4	0.5	0.5	0.4	0.4
Ischemic Heart Disease	0.8	0.7	0.7	0.7	0.8	0.7	0.7	0.7
Atrial Fibrillation	0.1	0.2	0.2	0.1	0.1	0.2	0.2	0.1
Stroke	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Hypertension	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Hyperlipidemia	1.0	1.0	1.0	1.0	0.9	1.0	1.0	1.0
Died in Year	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Restrict to New Patients with PCP visit w/in 30 Days							
Age	70.2	69.0	67.0	66.4	68.7	70.1	71.4	67.7
# Chronic Conditions	10.1	9.2	9.3	8.7	9.5	9.8	10.0	9.2
Male	0.5	0.4	0.4	0.4	0.4	0.4	0.3	0.4
White	0.7	0.7	0.8	0.7	0.8	0.7	0.7	0.7
Black	0.2	0.2	0.1	0.2	0.1	0.2	0.2	0.2
Hispanic	0.1	0.1	0.1	0.1	0.0	0.1	0.0	0.1
Disability or ESRD Medicare	0.3	0.4	0.4	0.5	0.3	0.4	0.3	0.4
AMI	0.2	0.1	0.1	0.0	0.1	0.1	0.1	0.1
Congestive Heart Failure	0.4	0.5	0.4	0.4	0.5	0.5	0.5	0.4
Ischemic Heart Disease	0.8	0.7	0.7	0.6	0.7	0.8	0.7	0.7
Atrial Fibrillation	0.2	0.2	0.2	0.2	0.1	0.2	0.2	0.2
Stroke	0.2	0.2	0.3	0.2	0.2	0.2	0.2	0.2
Hypertension	1.0	1.0	1.0	1.0	1.0	1.0	1.0	1.0
Hyperlipidemia	1.0	1.0	1.0	0.9	0.9	1.0	1.0	1.0
Died in Year	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Restrict to New Patients w/ no Prior Insulin Rx							
Age	70.9	70.5	62.5	68.8	70.8	71.4	68.6	69.4
# Chronic Conditions	11.1	9.6	7.2	8.7	9.6	10.2	7.8	8.9
Male	0.5	0.4	0.1	0.5	0.4	0.5	0.3	0.5
White	0.8	0.7	0.9	0.8	0.8	0.7	0.8	0.8
Black	0.2	0.1	0.0	0.1	0.1	0.1	0.2	0.1
Hispanic	0.1	0.1	0.1	0.0	0.0	0.1	0.0	0.1
Disability or ESRD Medicare	0.4	0.3	0.4	0.3	0.3	0.3	0.4	0.3
AMI	0.2	0.1	0.0	0.0	0.1	0.1	0.1	0.1
Congestive Heart Failure	0.5	0.5	0.1	0.3	0.5	0.5	0.2	0.4
Ischemic Heart Disease	0.9	0.8	0.3	0.7	0.8	0.8	0.6	0.6
Atrial Fibrillation	0.3	0.2	0.1	0.1	0.1	0.2	0.0	0.2
Stroke	0.2	0.2	0.1	0.2	0.2	0.2	0.1	0.1
Hypertension	1.0	1.0	1.0	0.9	1.0	1.0	1.0	1.0
Hyperlipidemia	1.0	1.0	1.0	1.0	1.0	1.0	0.8	1.0
Died in Year	0.0	0.0	0.0	0.0	0.0	0.0	0.0	0.0

Figure 3.1 Share of New Patients with a Previous Fill for a Diabetes Drug, by Drug Class and IV Assignment in 2011

Baseline Sample

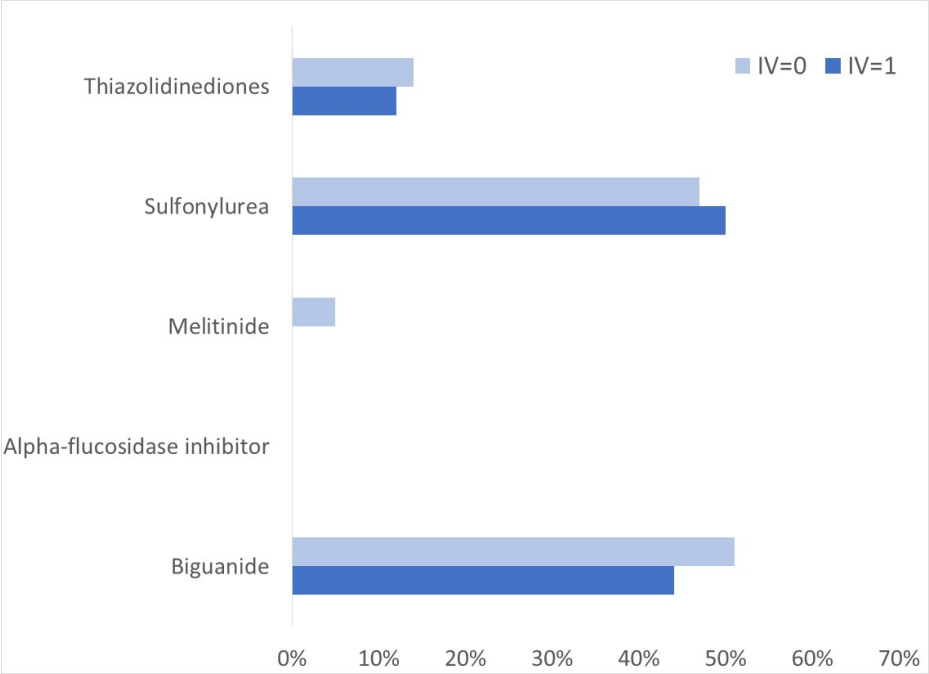


Restrict to New Patients with PCP visit w/in 30 Days



Continued

Restrict to New Patients w/ no Prior Insulin Rx



DISCUSSION

This paper examines an instrument for characterizing a specialist's penchant for prescribing novel treatments using treatment decisions for the physician's new patients. The motivating idea for this instrument is that the group of new patients are unlikely to systematically sort across specialists based on factors that are also related to outcomes of interest. I describe a framework for defining and assessing the sample of patients used to characterize the physician's treatment decisions. This framework also provides a set of descriptive analyses and empirical tests to examine the support for and against "randomness" of this sample. Using this framework, I assess the validity of an IV of this type in the context of diabetes medications. I find that the proposed IV performs inconsistently across measures examined. This highlights challenges associated with selecting a random sample of a physician's patients, a critical first step to

isolating physician preferences from beneficiary-level demand factors that influence treatment decisions.

The proposed instrument was not consistently related to the treatment of interest across sample definitions and years. This is a key assumption that must be met for an IV approach to identify a casual effect. Even when a strong and statistically significant relationship did exist, it was imprecisely estimated. This suggests exploring alternative definitions of the IV. Other options include measuring the share of new patients that fill a prescription for a novel drug. While this may be a better indicator of the physician's overall preference, it also faces certain challenges. In particular, depending on sample definition, specialists may see very few new patients in a year. As I imposed additional restrictions, the total sample of new patients for some endocrinologists was a single person. Thus, physicians could have very different assigned IV values driven by differences in the size of their populations of new patients.

The proposed instrument also did little to attenuate differences between patients under the care of physicians characterized as preferring novel diabetes drugs compared to those who were characterized as preferring conventional treatments. While we can control for these differences in our models, it raises concern that unobservable patient-level factors affecting demand for particular treatments remains.

Several prior studies have used measures of physician preferences as instruments for whether a patient receives a particular treatment. These are often in the context of identifying the effects of a prescription drug for certain populations or compared to other options when data from a randomized clinical trial are unavailable. This approach is less common in efforts to understand drivers of health care spending growth. This paper outlines considerations for implementing such an approach in this context, but further work in understanding the usefulness of such an approach remains.

The medical context for application examined in this paper is timely. As the number of medicines available to treat diabetes has increased, so have total utilization and spending in this therapeutic class. In 2014, spending on diabetic therapies in Medicare Part D totaled $14.1 billion, the highest amount of spending for Medicare Part D on any therapeutic class and an increase of 28 percent from the year before. In the same year, 126.1 million prescriptions for these drugs were filled, representing the fourth highest therapeutic class in terms of total volume and a 7.5 percent increase from 2013 (Medicare Payment Advisory Commission, 2017a). The rapid increase in spending on diabetic therapies has recently received attention. Decisions by drug makers to raise the price of insulins were the subject of several recent news articles (Belluz, 2017; Johnson, 2016; Picchi, 2017), prompted calls from the American Diabetes Association for a Congressional investigation (American Diabetes Association, 2016), and have been documented by researchers as well (Luo, Kesselheim, Greene, & Lipska, 2017). Examining physician prescribing patterns in this environment and whether they send a signal about broader trends in spending for other patients the physician treats would be useful in understanding the full implications of the use and adoption of drugs with high and rising costs.

Next steps should further examine the implications of varying sample definitions in ways described, but not demonstrated in this paper. In addition, the relationship between the instrument proposed here and outcomes of interest. For example, total spending for an endocrinologist's established diabetes patients, total spending for an endocrinologist's broader patient population, including the subset treated for particular conditions, such as thyroid disease or osteoporosis, and the use of other sets of services for these patients, such as imaging or lab tests.

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Appendix

Appendix 1

Identifying New Technologies

We used several mechanisms to identify the set of new medical technologies. We began by identifying non-drug services that were new and/or rapidly diffusing over our time period. First, we identified the 200 current procedural terminology (CPT) codes with the largest growth between 2005 and 2010 in Medicare claims data. From this list, we excluded coding changes and ancillary services. Then we added services identified by temporary CPT codes in any year between 2005 and 2010. A panel of four practicing physicians in the department of Health Care Policy (J. Michael McWilliams, Barbara McNeil, Nancy Keeting, and Bruce Landon) reviewed these lists and offered additional procedures and services for consideration. We then checked each service on the resulting list of candidate technologies against the American Medical Association's CPT guide to insure we identified all relevant CPT or International Classification of Diseases – 9th edition (ICD-9) procedure codes. Next, we counted the number of beneficiaries in medium and large provider organizations who had a claim for each service in 2011. We were interested in examining variation in use and so we needed services that were broadly adopted. Finally, we defined relevant denominator populations of beneficiaries who were eligible for the service. We excluded services if at least half of the provider organizations did not have at least 10 eligible beneficiaries. Our final set included 16 non-drug services.

We developed the list of new pharmaceutical products, including both physician-administered drugs and prescription drugs, using the following process. First, we identified all approved applications related to new drugs and biologics since 2005 using the Food & Drug Administration's (FDA) National Drug Code (NDC) database. From this list, we selected those

approvals for a new chemical entity, new molecular entity, new active ingredient, and all biologics. We did not select approvals of new combinations, formulations, or manufacturers. Only drugs approved between 2005 and 2010 were candidates for inclusion in the set of new pharmaceutical products for this study. This was consistent with the selection of non-drug services. Next, we identified unique active ingredients. We then examined the indication for each product and excluded those with indications not relevant to the Medicare population (such as contraceptives). In addition, we also excluded those approved for use as part of a service, such as a MRI or PET scan. We then counted the number of beneficiaries in medium sized provider organizations with claims for the drug and retained the drugs with at least 500 beneficiaries with claims in 2011, since we wished to capture drugs that are already approaching the flat portion of their diffusion curves. We also excluded drugs if at least half of the provider organizations in our sample did not have at least 10 eligible beneficiaries for the drug. Next, we identified physician-administered drugs using the most recent ASP NDC - HCPCS Crosswalk for Medicare Part B Drugs. Any drug not on that list was considered a prescription drug. There are 4 physician-administered drugs and 26 prescriptions drugs on the list.

Denominator populations

The set of patients eligible for each technology is the denominator population. These patients were identified using diagnoses codes. The relevant diagnoses were empirically determined by examining the diagnoses codes that appear in claims for the set of new drugs and services. First, we created a list of potential diagnoses for each drug and service. We did this by identifying all diagnoses on carrier line claims used to justify the non-drug service or physician-administered drug. For services performed in the inpatient setting we also created a list of the primary diagnoses listed on the claim that contained the service. For physician-administered

drugs and non-drug services appearing in the outpatient claims, we created a similar list with the primary diagnosis on the claim that contained the drug or service. Since Part D prescription drugs claims do not have diagnoses, we compiled all diagnoses appearing in the carrier claim lines for each beneficiary with a fill for a drug on our list of potential candidates. We then examined broad categories of ICD-9 codes and identified which broad categories appeared most frequently on the claim (or as the primary diagnoses on inpatient and outpatient claims). We made a determination whether to include the diagnosis based on how frequently it appeared and whether it was likely to be endogenous to the service or drug. For prescription drugs prescribed after a procedure, we also included the HCPCS codes for the indicated service. We confirmed that the denominator population criteria did not exclusively identify beneficiaries who had a claim for the drug or service. We then confirmed that at least 90% of beneficiaries with a claim for the drug or service were identified as being part of the denominator population.

Construction of provider organizations

We defined a provider organization as the physicians associated with a single tax identification number (TIN). Medicare beneficiaries were assigned to these organizations based on where they received a majority of primary care services. We implemented the SAS code used in other work within HCP, which included the following steps:

- Identified claims for primary care services as those with HCPCS codes equal to 99201 – 99215, G0402, G0438, and G0439.
- Identified claims by a primary care physician, i.e., those with specialty codes 01, 08, 11, or 38.
- Summed the number of primary care services performed by each primary care physician for each beneficiary

- Assigned each beneficiary to the TIN that includes the primary care physician responsible for the plurality of primary care services.

Appendix 2

Table A2.1 – Compounds and insulins approved for type-II diabetes

Class	Chemicals
biguanides	metformin
sulfonylureas	chlorpropamide glipizide glyburide glimepiride tolbutamide tolazamide
meglitinides	repaglinide nateglinide
alpha-glucosidase inhibitors	acarbose miglitol
thiazolidinediones	pioglitazone rosiglitazone
dipeptidyl peptidase IV inhibitors	sitagliptin linagliptin saxagliptin alogliptin
selective sodium-glucose transporter-2 inhibitors	canagliflozin empagliflozin dapagliflozin
insulins	lispro aspart glulisine detemir glargine degludec human
amylin analog	pramlintide
glucagonlike peptide-1 agonists	liraglutide exenatide dulaglutide albiglutide
bile acid sequestrants	colesevelam
dopamine agonists	bromocriptine

Table A2.2 – Odds Ratios Estimated for Logistic Regression Models of TZD and DOAC Prescribing for High TZD Prescribers

	Odds Ratio (95% CI)		
TZD prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Post-Alert Period	0.48 (0.47 to 0.48)***	0.47 (0.46 to 0.48)***	0.47 (0.46 to 0.48)***
Patients with Diabetes Rx[a]	0.80 (0.78 to 0.82)***	0.81 (0.79 to 0.83)***	0.82 (0.80 to 0.84)***
Age		1.00 (1.00 to 1.00)***	1.00 (1.00 to 1.00)***
Male		1.06 (1.04 to 1.08)***	1.06 (1.04 to 1.08)***
Disability or ERSD Medicare		0.90 (0.88 to 0.93)***	0.90 (0.88 to 0.93)***
# Chronic Conditions		1.02 (1.01 to 1.02)***	1.02 (1.01 to 1.02)***
Hypertension		1.04 (1.00 to 1.08)**	1.04 (1.01 to 1.08)**
Hyperlipidemia		1.21 (1.17 to 1.24)***	1.21 (1.17 to 1.24)***
Ischemic Heart Disease		0.93 (0.91 to 0.95)***	0.93 (0.91 to 0.95)***
Congestive Heart Failure		0.87 (0.85 to 0.89)***	0.87 (0.85 to 0.89)***
Stroke		0.92 (0.90 to 0.94)***	0.92 (0.90 to 0.95)***
Atrial Fibrillation		0.81 (0.78 to 0.83)***	0.81 (0.78 to 0.83)***
AMI		0.81 (0.78 to 0.84)***	0.81 (0.78 to 0.84)***
State Fixed Effects	no	no	yes
Physician-Specific Effects			
Pre-period (std. dev.)	0.36	0.35	0.34
Post-period (std. dev.)	0.48	0.48	0.48
Pre- and post-period corr.	0.11	0.09	0.08
PCPs, No.	5,602	5,366	5,301
Obs	1,247,778	1,119,852	1,103,393

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Continued

	Odds Ratio (95% CI)		
DOAC prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Response to Alert	0.98 (0.92 to 1.05)	0.99 (0.93 to 1.06)	0.98 (0.92 to 1.05)
Pre-Alert TZD Rx	1.15 (1.07 to 1.24)***	1.14 (1.06 to 1.24)***	1.14 (1.06 to 1.23)***
Patients with Anticoagulant Rx[a]	0.95 (0.91 to 1.00)**	0.94 (0.89 to 0.99)**	0.97 (0.92 to 1.02)
Age		1.00 (0.99 to 1.01)	1.00 (0.99 to 1.01)
Male		1.05 (0.94 to 1.17)	1.04 (0.93 to 1.16)
Disability or ERSD Medicare		0.62 (0.52 to 0.73)***	0.63 (0.53 to 0.74)***
# Chronic Conditions		1.04 *1.02 to 1.05)***	1.04 (1.02 to 1.05)***
State Fixed Effects	no	no	yes
PCPs, No.	5,602	5,366	5,282
Obs	278,283	264,384	261,207

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Table A2.3 – Odds Ratios Estimated for Logistic Regression Models of Rosiglitazone and DOAC Prescribing

	Odds Ratio (95% CI)		
rosiglitazone prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Post-Alert Period	0.06 (0.06 to 0.06)***	0.06 (0.05 to 0.06)***	0.05 (o.o5 to 0.06)***
Total Diabetes Rx[a]	1.17 (1.16 to 1.18)***	1.19 (1.17 to 1.20)***	1.16 (1.15 to 1.18)***
Age		0.99 (0.99 to 0.99)***	0.99 (0.99 to 0.99)***
Male		1.07 (10.5 to 1.09)***	1.07 (1.05 to 1.09)***
Disability or ERSD Medicare		0.89 (0.87 to 0.91)***	0.89 (0.87 to 0.91)***
# Chronic Conditions		1.02 (1.02 to 1.02)***	1.02 (1.01 to 1.02)***
Hypertension		1.02 (0.99 to 1.06)	1.03 (1.00 to 1.06)*
Hyperlipidemia		1.24 (1.21 to 1.27)***	1.24 (1.21 to 1.28)***
Ischemic Heart Disease		0.91 (0.89 to 0.93)***	0.91 (0.89 to 0.93)***
Congestive Heart Failure		0.87 (0.85 to 0.89)***	0.87 (0.85 to 0.89)***
Stroke		0.93 (0.91 to 0.95)***	0.93 (0.90 to 0.95)***
Atrial Fibrillation		0.79 (0.77 to 0.81)***	0.79 (0.77 to 0.81)***
AMI		0.78 (0.75 to 0.81)***	0.78 (0.75 to 0.81)***
State Fixed Effects	no	no	yes
Physician-Specific Effects			
Pre-period (std. dev.)	1.47	1.50	1.48
Post-period (std. dev.)	2.11	2.16	2.16
Pre- and post-period corr.	-0.02	-0.02	-0.02
PCPs, No.	69,697	69,618	68,984
Bene-Month Obs.	6,121,681	5,617,706	5,540,841

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Continued

	Odds Ratio (95% CI)		
DOAC prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Response to Alert	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)	1.00 (0.98 to 1.02)
Pre-Alert TZD Rx	1.09 (1.07 to 1.12)***	1.08 (1.05 to 1.10)***	1.06 (1.04 to 1.09)***
Patients with Anticoagulant Rx[a]	0.97 (0.96 to 0.99)***	0.97 (0.96 to 0.98)***	0.98 (0.96 to 0.99)***
Age[a]		1.00 (0.99 to 1.00)***	1.00 (0.99 to 1.00)**
Male		1.04 (1.00 to 1.08)*	1.04 (1.00 to 1.08)*
Disability or ERSD Medicare		0.6 (0.56 to 0.64)***	0.59 (0.55 to 0.63)***
# Chronic Conditions		1.04 (1.03 to 10.4)***	1.03 (1.03 to 1.04)***
State Fixed Effects	no	yes	yes
PCPs, No.	69,697	69,618	68,981
Obs	2,206,857	2,205,473	2,192,397

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Table A2.4 – Odds Ratios Estimated for Logistic Regression Models of TZD and DOAC Prescribing Including Post-Period-Chronic Conditions Interactions

	Odds Ratio (95% CI)		
TZD prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Post-Alert Period		0.59 (0.57 to 0.60)***	0.59 (0.58 to 0.60)***
Total Diabetes Rx[a]		1.07 (1.06 to 1.08)***	1.06 (1.05 to 1.07)***
Age		0.99 (0.99 to 0.99)***	0.99 (0.99 to 0.99)***
Male		1.09 (1.08 to 1.10)***	1.09 (1.08 to 1.10)***
Disability or ERSD Medicare		0.88 (0.87 to 0.89)***	0.88 (0.86 to 0.89)***
# Chronic Conditions		1.02 (1.02 to 1.02)***	1.02 (1.02 to 1.02)***
Hypertension		1.04 (1.02 to 1.07)***	1.04 (1.02 to 1.07)***
Hyperlipidemia		1.27 (1.25 to 1.30)***	1.27 (1.25 to 1.30)***
Ischemic Heart Disease		0.95 (0.93 to 0.96)***	0.94 (0.93 to 0.96)***
Congestive Heart Failure		0.88 (0.88 to 0.89)***	0.88 (0.87 to 0.90)***
Stroke		0.93 (0.91 to 0.94)***	0.93 (0.91 to 0.94)***
Atrial Fibrillation		0.83 (0.81 to 0.84)***	0.93 (0.91 to 0.96)***
AMI		0.82 (0.80 to 0.85)***	0.82 (0.80 to 0.84)***
Hypertension*Post		0.96 (0.94 to 0.99)***	0.96 (0.94 to 0.99)***
Hyperlipidemia*Post		0.98 (0.96 to 1.00)*	0.98 (0.96 to 1.00)*
Ischemic Heart Disease*Post		0.94 (0.93 to 0.96)***	0.94 (0.93 to 0.96)***
Congestive Heart Failure*Post		0.91 (0.90 to 0.93)***	0.91 (0.89 to 0.93)***
Stroke*Post		0.97 (0.95 to 1.00)**	0.97 (0.95 to 0.99)**
Atrial Fibrillation*Post		0.94 (0.91 to 0.96)***	0.83 (0.81 to 0.84)***
AMI*Post		0.95 (0.92 to 0.99)***	0.95 (0.92 to 0.99)***
State Fixed Effects	no	no	yes
Physician-Specific Effects			
Pre-period (std. dev.)		0.94	0.93
Post-period (std. dev.)		0.85	0.85
Pre- and post-period corr.		-0.18	-0.19
PCPs, No.		69,618	68,984
Bene-month observations		5,617,706	5,540,841

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Continued

	Odds Ratio (95% CI)		
DOAC prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Response to Alert		1.01 (0.99 to 1.04)	1.02 (0.99 to 1.04)
Pre-Alert TZD Rx		1.11 (1.09 to 1.14)***	1.09 (1.07 to 1.12)***
Patients with Anticoagulant Rx[a]		0.97 (0.96 to 0.98)***	0.98 (0.97 to 0.99)***
Age		1.00 (0.99 to 1.00)***	1.00 (1.00 to 1.00)**
Male		1.04 (0.99 to 1.08)*	1.04 (1.00 to 1.08)*
Disability or ERSD Medicare		0.60 (0.56 to 0.64)***	0.59 (0.55 to 0.63)***
# Chronic Conditions		1.03 (1.03 to 1.04)***	1.03 (1.03 to 104)***
State Fixed Effects		no	yes
PCPs, No.		69,618	68,981
Obs		2,205,473	2,192,397

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Table A2.5 – Odds Ratios for Logistic Regression Model of DOAC Prescribing in December 2011

	Odds Ratio (95% CI)		
DOAC prescribing	**Baseline model**	**Adjusted for beneficiary characteristics**	**Adjusted for beneficiary characteristics and physician state**
Response to Alert	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)	1.01 (0.99 to 1.03)
Pre-Alert TZD Rx	1.14 (1.12 to 1.17)***	1.12 (1.10 to 1.15)***	1.10 (1.08 to 1.13)***
Patients with Anticoagulant Rx[a]	0.97 (0.96 to 0.99)***	0.97 (0.95 to 0.98)***	0.98 (0.96 to 0.99)***
Age		0.96 (0.04 to 0.99)***	0.97)0.94 to 0.99)**
Male		1.03 (0.99 to 1.07)	1.03 (0.99 to 1.07)
Disability or ERSD Medicare		0.60 (0.56 to 0.64)***	0.59 (0.54 to 0.63)***
# Chronic Conditions		1.03 (1.03 to 1.04)***	1.03 (1.03 to 1.04)***
State Fixed Effects	no	no	yes
PCPs, No.	64,073	64,005	63,454
Bene-Month Obs	192	191,528	190,403

* p<0.10
** p<0.05
***p<0.01

[a] Variable is scaled by its standard deviation

Appendix 3

Table A3.1 Share of New Patients with Previous Prescription for a Diabetes Drug, by Drug Class

New Patients in 2011			
Share of New Patients with Previous Rx in Drug Class	**Full Sample**	**IV=1**	**IV=0**
Baseline Sample			
Biguanide	0.38	0.49	0.36
Alpha-flucosidase inhibitor	0.00	0.01	0.00
Insulin	0.47	0.37	0.49
Melitinide	0.02	0.01	0.02
Sulfonylurea	0.34	0.39	0.33
Thiazolidinediones	0.09	0.12	0.09
Restrict to New Patients with PCP visit w/in 30 Days			
Biguanide	0.35	0.39	0.34
Alpha-flucosidase inhibitor	0.00	0.00	0.00
Insulin	0.51	0.41	0.53
Melitinide	0.03	0.00	0.04
Sulfonylurea	0.35	0.35	0.35
Thiazolidinediones	0.07	0.06	0.07
Restrict to New Patients w/ no Prior Insulin Rx			
Biguanide	0.50	0.44	0.51
Alpha-flucosidase inhibitor	0.00	0.00	0.00
Melitinide	0.04	0.00	0.05
Sulfonylurea	0.47	0.50	0.47
Thiazolidinediones	0.14	0.12	0.14